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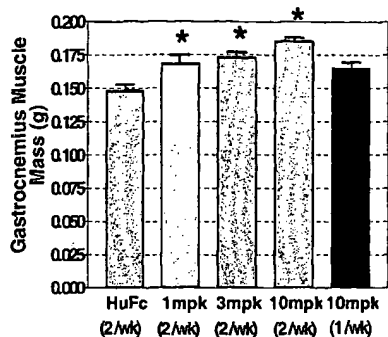
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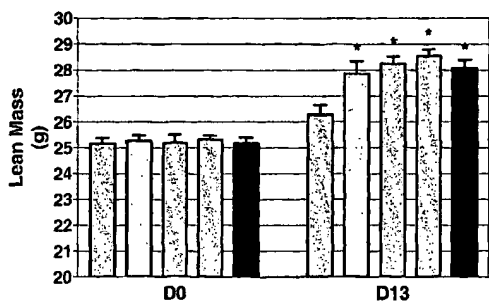
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(54) Title: **BINDING AGENTS WHICH INHIBIT MYOSTATIN**



A



B

(57) Abstract: The present invention provides binding agents comprising peptides capable of binding myostatin and inhibiting its activity. In one embodiment the binding agent comprises at least one myostatin-binding peptide attached directly or indirectly to at least one vehicle such as a polymer or an Fc domain. The binding agents of the present invention produced increased lean muscle mass when administered to animals and decreased fat to muscle ratios. Therapeutic compositions containing the binding agents of the present invention are useful for treating muscle-wasting disorders and other metabolic disorders including diabetes and obesity.

Legend:
HuFc
1mpk
3mpk
10mpk (2/wk)
10mpk (1/wk)



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BINDING AGENTS WHICH INHIBIT MYOSTATIN

This application hereby claims benefit of United States provisional application serial number 60/435,923, filed December 20, 2002, the entire disclosure of which is relied upon and
5 incorporated by reference.

FIELD OF THE INVENTION

The invention relates to growth factors and in particular to the growth factor myostatin and agents which bind myostatin and inhibit its activity.

BACKGROUND

Myostatin, also known as growth/differentiation factor 8 (GDF-8), is a transforming growth factor- β (TGF- β) family member known to be involved in regulation of skeletal muscle mass. Most members of the TGF- β -GDF family are expressed non-specifically in many tissue types and exert a variety of pleiotrophic actions. However, myostatin is largely expressed in
15 cells of developing and adult skeletal muscle tissue and plays an essential role in negatively controlling skeletal muscle growth (McPherron et al. *Nature* (London) **387**, 83-90 (1997)). Recent studies, however, indicate that low levels of myostatin expression can be measured in cardiac, adipose and pre-adipose tissues.

The myostatin protein has been highly conserved evolutionarily (McPherron et al. *PNAS*
20 *USA* **94**:12457-12461 (1997)). The biologically active C-terminal region of myostatin has 100 percent sequence identity between human, mouse, rat, cow, chicken, and turkey sequences. The function of myostatin also appears to be conserved across species as well. This is evident from the phenotypes of animals having a mutation in the myostatin gene. Two breeds of cattle, the Belgian Blue (Hanset R., *Muscle Hypertrophy of Genetic Origin and its Use to Improve Beef*
25 *Production*, eds, King, J.W.G. & Menissier, F. (Nijhoff, The Hague, The Netherlands) pp. 437-449) and the Piedmontese (Masoero, G. & Poujardieu, B, *Muscle Hypertrophy of Genetic Origin and its Use to Improve Beef Production*., eds, King, J.W.G. & Menissier, F. (Nijhoff, The
Hague, The Netherlands) pp. 450-459) are characterized by a "double muscling" phenotype and increase in muscle mass. These breeds were shown to contain mutations in the coding region of
30 the myostatin gene (McPherron et al. (1997) *supra*). In addition, mice containing a targeted deletion of the gene encoding myostatin (*Mstn*) demonstrate a dramatic increase in muscle mass without a corresponding increase in fat. Individual muscles of *Mstn*^{-/-} mice weigh approximately 100 to 200 percent more than those of control animals as a result of muscle fiber hypertrophy and hyperplasia (Zimmers et al. *Science* **296**, 1486 (2002)).

Administration of myostatin to certain strains of mice has been shown to create a condition similar to muscle wasting disorders found associated with cancer, AIDS, and muscular dystrophy, for example. Myostatin administered as myostatin-producing CHO cells to athymic nude mice resulted in a wasting effect with a high degree of weight loss, a decrease of as much as 50% of skeletal muscle mass in addition to fat wasting, and severe hypoglycemia (Zimmers et al. *supra*).

Loss of myostatin appears to result in the retention of muscle mass and reduction in fat accumulation with aging. It has been shown that age-related increases in adipose tissue mass and decrease in muscle mass were proportional to myostatin levels, as determined by a comparison of fat and muscle mass in Mstn^{+/+} when compared with Mstn^{-/-} adult knockout mice (McFerron et al. *J. Clin. Invest* 109, 595 (2002)). Mstn^{-/-} mice showed decreased fat accumulation with age compared with Mstn^{+/+} mice.

In addition myostatin may play a role in maintaining blood glucose levels and may influence the development of diabetes in certain cases. It is known that, for example, skeletal muscle resistance to insulin-stimulated glucose uptake is the earliest known manifestation of non-insulin-dependent (type 2) diabetes mellitus (Corregan et al. *Endocrinology* 128:1682 (1991)). It has now been shown that the lack of myostatin partially attenuates the obese and diabetes phenotypes of two mouse models, the agouti lethal yellow (A^y) (Yen et al. *FASEB J.* 8:479 (1994)), and obese (Lep^{ob/ob}). Fat accumulation and total body weight of the A^{y/a}, Mstn^{-/-} double mutant mouse was dramatically reduced compared with the A^{y/a} Mstn^{+/+} mouse (McFerron et al., (2002) *supra*). In addition, blood glucose levels in the A^{y/a}, Mstn^{-/-} mice was dramatically lower than in A^{y/a} Mstn^{+/+} mice following exogenous glucose load, indicating that the lack of myostatin improved glucose metabolism. Similarly Lep^{ob/ob} Mstn^{-/-} mice showed decreased fat accumulation when compared with the Lep^{ob/ob} Mstn^{+/+} phenotype.

Therefore, there is considerable evidence from the phenotypes of over-expressing and knockout animals that myostatin may play a role in contributing to a number of metabolic disorders including disorders resulting in muscle wasting, diabetes, obesity and hyperglycemia.

SUMMARY OF THE INVENTION

The present invention is directed to binding agents which bind myostatin and inhibit its activity. The binding agents comprise at least one peptide capable of binding myostatin. The myostatin-binding peptides are preferably between about 5 and about 50 amino acids in length, more preferably between about 10 and 30 amino acids in length, and most preferably between about 10 and 25 amino acids in length. In one embodiment the myostatin-binding peptide comprises the amino acid sequence WMCPP (SEQ ID NO: 633). In another embodiment the

myostatin binding peptides comprise the amino acid sequence C_{a1}a₂Wa₃WMCPP (SEQ ID NO: 352), wherein a₁, a₂ and a₃ are selected from a neutral hydrophobic, neutral polar, or basic amino acid. In another embodiment the myostatin binding peptide comprises the sequence Cb₁b₂Wb₃WMCPP (SEQ ID NO: 353), wherein b₁ is selected from any one of the amino acids T, I, or R; b₂ is selected from any one of R, S, Q; b₃ is selected from any one of P, R and Q, and wherein the peptide is between 10 and 50 amino acids in length, and physiologically acceptable salts thereof. In another embodiment, the myostatin binding peptide comprises the formula:

c₁c₂c₃c₄c₅c₆Cc₇c₈Wc₉WMCPPc₁₀c₁₁c₁₂c₁₃ (SEQ ID NO: 354), wherein:

- c₁ is absent or any amino acid;
- c₂ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
- c₃ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
- c₄ is absent or any amino acid;
- c₅ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
- c₆ is absent or a neutral hydrophobic, neutral polar, or basic amino acid;
- c₇ is a neutral hydrophobic, neutral polar, or basic amino acid;
- c₈ is a neutral hydrophobic, neutral polar, or basic amino acid;
- c₉ is a neutral hydrophobic, neutral polar or basic amino acid; and
- c₁₀ to c₁₃ is any amino acid; and wherein the peptide is between 20 and 50 amino acids in length, and physiologically acceptable salts thereof.

A related embodiment the myostatin binding peptide comprises the formula:

d₁d₂d₃d₄d₅d₆Cd₇d₈Wd₉WMCPPd₁₀d₁₁d₁₂d₁₃ (SEQ ID NO: 355), wherein

- d₁ is absent or any amino acid;
 - d₂ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 - d₃ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 - d₄ is absent or any amino acid;
 - d₅ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 - d₆ is absent or a neutral hydrophobic, neutral polar, or basic amino acid;
 - d₇ is selected from any one of the amino acids T, I, or R;
 - d₈ is selected from any one of R, S, Q;
 - d₉ is selected from any one of P, R and Q, and
 - d₁₀ to d₁₃ is selected from any amino acid,
- and wherein the peptide is between 20 and 50 amino acids in length, and physiologically acceptable salts thereof.

Additional embodiments of binding agents comprise at least one of the following peptides:

(1) a peptide capable of binding myostatin, wherein the peptide comprises the sequence

WYe₁e₂Ye₃G, (SEQ ID NO: 356)

wherein e₁ is P, S or Y,
e₂ is C or Q, and

e_3 is G or H, wherein the peptide is between 7 and 50 amino acids in length, and physiologically acceptable salts thereof;

(2) a peptide capable of binding myostatin, wherein the peptide comprises the sequence $f_1\text{EML}f_2\text{SL}f_3f_4\text{LL}$, (SEQ ID NO: 455),

5 wherein f_1 is M or I,
 f_2 is any amino acid,
 f_3 is L or F,
 f_4 is E, Q or D;
 and wherein the peptide is between 7 and 50 amino acids in length, and physiologically
 10 acceptable salts thereof;

(3) a peptide capable of binding myostatin wherein the peptide comprises the sequence $Lg_1g_2\text{LL}g_3g_4\text{L}$, (SEQ ID NO: 456), wherein

15 g_1 is Q, D or E,
 g_2 is S, Q, D or E,
 g_3 is any amino acid,
 g_4 is L, W, F, or Y, and wherein the peptide is between 8 and 50 amino acids in length,
 and physiologically acceptable salts thereof;

(4) a peptide capable of binding myostatin, wherein the peptide comprises the sequence $h_1h_2h_3h_4h_5h_6h_7h_8h_9$ (SEQ ID NO: 457), wherein

20 h_1 is R or D,
 h_2 is any amino acid,
 h_3 is A, T S or Q,
 h_4 is L or M,
 h_5 is L or S,
 25 h_6 is any amino acid,
 h_7 is F or E,
 h_8 is W, F or C,
 h_9 is L, F, M or K, and wherein the peptide is between 9 and 50 amino acids in length,
 and physiologically acceptable salts thereof.

30 In one embodiment, the binding agents of the present invention further comprise at least one vehicle such as a polymer or an Fc domain, and may further comprise at least one linker sequence. In this embodiment, the binding agents of the present invention are constructed so that at least one myostatin-binding peptide is attached to at least one vehicle. The peptide or peptides are attached directly or indirectly through a linker sequence, to the vehicle at the N-terminal, C-
 35 terminal or an amino acid sidechain of the peptide. In this embodiment, the binding agents of the present invention have the following generalized structure:

$(X^1)_a\text{-F}^1\text{-(X}^2)_b$, or multimers thereof;

wherein F^1 is a vehicle; and X^1 and X^2 are each independently selected from

$\text{-(L}^1)_c\text{-P}^1$;

40 $\text{-(L}^1)_c\text{-P}^1\text{-(L}^2)_d\text{-P}^2$;

$-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$;

and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$;

wherein P^1 , P^2 , P^3 , and P^4 are peptides capable of binding myostatin; and

L^1 , L^2 , L^3 , and L^4 are each linkers; and a, b, c, d, e, and f are each independently 0 or 1,

5 provided that at least one of a and b is 1, and physiologically acceptable salts thereof.

In various embodiments of binding agents having this generalized structure, the peptides P^1 , P^2 , P^3 , and P^4 can be independently selected from one or more of any of the peptides comprising the sequences provided above. P^1 , P^2 , P^3 , and P^4 are independently selected from one or more peptides comprising any of the following sequences: SEQ ID NO: 633, SEQ ID NO: 352, SEQ ID NO: 353, SEQ ID NO: 354, SEQ ID NO: 355, SEQ ID NO: 356, SEQ ID NO: 455, SEQ ID NO: 456, or SEQ ID NO: 457.

In a further embodiment, the binding agents comprise peptides fused to an Fc domain, either directly or indirectly, thereby providing peptibodies. The peptibodies of the present invention display a high binding affinity for myostatin and can inhibit the activity of myostatin as demonstrated both *in vitro* using cell based assays and in animals.

The present invention also provides nucleic acid molecules comprising polynucleotides encoding the peptides, peptibodies, and peptide and peptibody variants and derivatives of the present invention.

20 The present invention provides pharmaceutically acceptable compositions comprising one or more binding agents of the present invention.

The binding agents of the present invention inhibit myostatin activity *in vitro* and *in vivo*. The binding agents of the present invention increase lean muscle mass in a treated animal and decreases fat mass as a percentage of body weight of the animal. The myostatin binding agents of the present invention increase muscular strength in treated animal models.

The present invention provides methods of inhibiting myostatin activity in animals including humans by administering an effective dosage of one or more binding agents to the subject. The present invention provides methods of increasing lean muscle mass in animals including humans by administering an effective dosage of one or more binding agents. The present invention further provides methods of treating myostatin-related disorders by administering an therapeutically effective dosage of one or more myostatin binding agents in a pharmaceutically acceptable composition to a subject. The present invention provides methods of treating muscle wasting disorders including muscular dystrophy, muscle wasting due to cancer, AIDS, rheumatoid arthritis, renal failure, uremia, chronic heart failure, age-related sarcopenia, prolonged bed-rest, spinal chord injury, stroke, bone fracture. The present invention also provides

methods of treating metabolic disorders including obesity, diabetes, hyperglycemia, and bone loss.

The present invention also provides a method of increasing muscle mass in food animals by administering an effective dosage of one or more myostatin binding agents to the animal.

5 The present invention provides assays utilizing one or more myostatin binding agents to identify and quantitate myostatin in a sample. The assays may be diagnostic assays for measuring or monitoring myostatin levels in individuals with a myostatin related disorder or disease.

BRIEF DESCRIPTION OF THE FIGURES

10 Figure 1 shows myostatin activity as measured by expressed luciferase activity (y-axis) vrs. concentration (x-axis) for the TN8-19 peptide QGHCTRWPWMCPY (Seq ID No: 32) and the TN8-19 peptibody (pb) to determine the IC₅₀ for each using the C2C12 pMARE luciferase assay described in the Examples below. The peptibody has a lower IC₅₀ value compared with the peptide.

15 Figure 2 is a graph showing the increase in total body weight for CD1 nu/nu mice treated with increasing dosages of the 1x mTN8-19-21 peptibody over a fourteen day period compared with mice treated with a huFc control, as described in Example 8.

Figure 3A shows the increase in the mass of the gastrocnemius muscle mass at necropsy of the mice treated in Figure 2 (Example 8). Figure 3B shows the increase in lean mass as
20 determined by NMR on day 0 compared with day 13 of the experiment described in Example 8.

Figure 4 shows the increase in lean body mass as for CD1 nu/nu mice treated with biweekly injections of increasing dosages of 1x mTN8-19-32 peptibody as determined by NMR on day 0 and day 13 of the experiment described in Example 8.

Figure 5A shows the increase in body weight for CD1 nu/nu mice treated with biweekly
25 injections of 1x mTN8-19-7 compared with 2x mTN8-19-7 and the control animal for 35 days as described in Example 8. Figure 5B shows the increase in lean carcass weight at necropsy for the 1x and 2x versions at 1 mg/kg and 3 mg/kg compared with the animals receiving the vehicle (huFc) (controls).

Figure 6A shows the increase in lean muscle mass vrs. body weight for aged *mdx* mice
30 treated with either affinity matured 1x mTN8-19-33 peptibody or huFc vehicle at 10 mg/kg subcutaneously every other day for three months. Figure 6B shows the change in fat mass compared to body weight as determined by NMR for the same mice after 3 months of treatment.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides binding agents capable of binding myostatin and inhibiting its activity. The myostatin binding agents can be used in assays, to identify, quantitate, or monitor the level of myostatin in an animal. The myostatin binding agents of the present invention reduce myostatin activity. The myostatin binding agents of the present invention increase lean muscle mass in animals, decrease fat mass as a percentage of body weight, and increase muscle strength. The myostatin binding agents of the present invention can be used to treat a variety of metabolic disorders in which myostatin plays a role, including muscle wasting disorders such as muscular dystrophies, muscle wasting due to cancer, AIDS, rheumatoid arthritis, renal failure, uremia, chronic heart failure, prolonged bed-rest, spinal chord injury, stroke, and age-related sarcopenia as well as other metabolic disorders including diabetes, obesity, hyperglycemia, and bone loss, by administering a therapeutic dosage of one or more binding agents in a pharmaceutically acceptable composition to a subject.

Myostatin

Myostatin, a growth factor also known as GDF-8, is known to be a negative regulator of skeletal muscle tissue. Myostatin is synthesized as an inactive preproprotein which is activated by proteolytic cleavage (Zimmers et al., *supra* (2002)). The precursor protein is cleaved to produce an NH₂-terminal inactive prodomain and an approximately 109 amino acid COOH-terminal protein in the form of a homodimer of about 25 kDa, which is the mature, active form (Zimmers et al, *supra* (2002)). It is now believed that the mature dimer circulates in the blood as an inactive latent complex bound to the propeptide (Zimmers et al, *supra* (2002)).

As used herein the term "full-length myostatin" refers to the full-length human preproprotein sequence described in McPherron et al. *supra* (1997), as well as related full-length polypeptides including allelic variants and interspecies homologs which are also described in McPherron et al. (1997). As used herein, the term "prodomain" or "propeptide" refers to the inactive NH₂-terminal protein which is cleaved off to release the active COOH-terminal protein. As used herein the term "myostatin" or "mature myostatin" refers to the mature, biologically active COOH-terminal polypeptide, in monomer, dimer, multimeric form or other form. "Myostatin" or "mature myostatin" also refers to fragments of the biologically active mature myostatin, as well as related polypeptides including allelic variants, splice variants, and fusion peptides and polypeptides. The mature myostatin COOH-terminal protein has been reported to have 100% sequence identity among many species including human, mouse, chicken, porcine, turkey, and rat (Lee et al., *PNAS* 98, 9306 (2001)). Myostatin may or may not include additional

terminal residues such as targeting sequences, or methionine and lysine residues and /or tag or fusion protein sequences, depending on how it is prepared.

As used herein the term “capable of binding to myostatin” or “having a binding affinity for myostatin” refers to a binding agent or peptide which binds to myostatin as demonstrated by
5 as the phage ELISA assay, the BIAcore® or KinExA™ assays described in the Examples below.

As used herein, the term “capable of modifying myostatin activity” refers to the action of an agent as either an agonist or an antagonist with respect to at least one biological activity of myostatin. As used herein, “agonist” or “mimetic” activity refers an agent having biological activity comparable to a protein that interacts with the protein of interest, as described, for
10 example, in International application WO 01/83525, filed May 2, 2001, which is incorporated herein by reference.

As used herein, the term “inhibiting myostatin activity” or “having antagonist activity” refers to the ability of a peptide or binding agent to reduce or block myostatin activity or signaling as demonstrated or *in vitro* assays such as, for example, the pMARE C2C12 cell-based
15 myostatin activity assay or by *in vivo* animal testing as described below.

Structure of Myostatin Binding Agents

In one embodiment, the binding agents of the present invention comprise at least one myostatin binding peptide covalently attached to at least one vehicle such as a polymer or an Fc
20 domain. The attachment of the myostatin-binding peptides to at least one vehicle is intended to increase the effectiveness of the binding agent as a therapeutic by increasing the biological activity of the agent and/or decreasing degradation *in vivo*, increasing half-life *in vivo*, reducing toxicity or immunogenicity *in vivo*. The binding agents of the present invention may further comprise a linker sequence connecting the peptide and the vehicle. The peptide or peptides are
25 attached directly or indirectly through a linker sequence to the vehicle at the N-terminal, C-terminal or an amino acid sidechain of the peptide. In this embodiment, the binding agents of the present invention have the following structure:

$(X^1)_a-F^1-(X^2)_b$, or multimers thereof;

wherein F^1 is a vehicle; and X^1 and X^2 are each independently selected from

30 $-(L^1)_c-P^1$;

$-(L^1)_c-P^1-(L^2)_d-P^2$;

$-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$;

and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$;

wherein P^1 , P^2 , P^3 , and P^4 are peptides capable of binding myostatin; and

L¹, L², L³, and L⁴ are each linkers; and a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1.

Any peptide containing a cysteinyl residue may be cross-linked with another Cys-containing peptide, either or both of which may be linked to a vehicle. Any peptide having more than one Cys residue may form an intrapeptide disulfide bond, as well.

In one embodiment, the vehicle is an Fc domain, defined below. This embodiment is referred to as a "peptibody". As used herein, the term "peptibody" refers to a molecule comprising an antibody Fc domain attached to at least one peptide. The production of peptibodies is generally described in PCT publication WO 00/24782, published May 4, 2000, which is herein incorporated by reference. Exemplary peptibodies are provided as 1x and 2x configurations with one copy and two copies of the peptide (attached in tandem) respectively, as described in the Examples below.

Peptides

As used herein the term "peptide" refers to molecules of about 5 to about 90 amino acids linked by peptide bonds. The peptides of the present invention are preferably between about 5 to about 50 amino acids in length, more preferably between about 10 and 30 amino acids in length, and most preferably between about 10 and 25 amino acids in length, and are capable of binding to the myostatin protein.

The peptides of the present invention may comprise part of a sequence of naturally occurring proteins, may be randomized sequences derived from naturally occurring proteins, or may be entirely randomized sequences. The peptides of the present invention may be generated by any methods known in the art including chemical synthesis, digestion of proteins, or recombinant technology. Phage display and RNA-peptide screening, and other affinity screening techniques are particularly useful for generating peptides capable of binding myostatin.

Phage display technology is described, for example, in Scott *et al.* *Science* 249: 386 (1990); Devlin *et al.*, *Science* 249: 404 (1990); U.S. Patent No. 5,223,409, issued June 29, 1993; U.S. Patent No. 5,733,731, issued March 31, 1998; U.S. Patent No. 5,498,530, issued March 12, 1996; U.S. Patent No. 5,432,018, issued July 11, 1995; U.S. Patent No. 5,338,665, issued August 16, 1994; U.S. Patent No. 5,922,545, issued July 13, 1999; WO 96/40987, published December 19, 1996; and WO 98/15833, published April 16, 1998, each of which is incorporated herein by reference. Using phage libraries, random peptide sequences are displayed by fusion with coat proteins of filamentous phage. Typically, the displayed peptides are affinity-eluted either specifically or non-specifically against the target molecule. The retained phages may be enriched

by successive rounds of affinity purification and repropagation. The best binding peptides are selected for further analysis, for example, by using phage ELISA, described below, and then sequenced. Optionally, mutagenesis libraries may be created and screened to further optimize the sequence of the best binders (Lowman, *Ann Rev Biophys Biomol Struct* 26:401-24 (1997)).

5 Other methods of generating the myostatin binding peptides include additional affinity selection techniques known in the art. A peptide library can be fused in the carboxyl terminus of the lac repressor and expressed in *E.coli*. Another *E. coli*-based method allows display on the cell's outer membrane by fusion with a peptidoglycan-associated lipoprotein (PAL). Hereinafter, these and related methods are collectively referred to as "*E. coli* display." In another method, 10 translation of random RNA is halted prior to ribosome release, resulting in a library of polypeptides with their associated RNA still attached. Hereinafter, this and related methods are collectively referred to as "ribosome display." Other methods employ chemical linkage of peptides to RNA. See, for example, Roberts and Szostak, *Proc Natl Acad Sci USA*, 94: 12297-303 (1997). Hereinafter, this and related methods are collectively referred to as "RNA-peptide 15 screening." Yeast two-hybrid screening methods also may be used to identify peptides of the invention that bind to myostatin. In addition, chemically derived peptide libraries have been developed in which peptides are immobilized on stable, non-biological materials, such as polyethylene rods or solvent-permeable resins. Another chemically derived peptide library uses photolithography to scan peptides immobilized on glass slides. Hereinafter, these and related 20 methods are collectively referred to as "chemical-peptide screening." Chemical-peptide screening may be advantageous in that it allows use of D-amino acids and other analogues, as well as non-peptide elements. Both biological and chemical methods are reviewed in Wells and Lowman, *Curr Opin Biotechnol* 3: 355-62 (1992).

25 Additionally, selected peptides capable of binding myostatin can be further improved through the use of "rational design". In this approach, stepwise changes are made to a peptide sequence and the effect of the substitution on the binding affinity or specificity of the peptide or some other property of the peptide is observed in an appropriate assay. One example of this technique is substituting a single residue at a time with alanine, referred to as an "alanine walk" or an "alanine scan". When two residues are replaced, it is referred to as a "double alanine walk". 30 The resultant peptide containing amino acid substitutions are tested for enhanced activity or some additional advantageous property.

In addition, analysis of the structure of a protein-protein interaction may also be used to suggest peptides that mimic the interaction of a larger protein. In such an analysis, the crystal structure of a protein may suggest the identity and relative orientation of critical residues of the 35 protein, from which a peptide may be designed. See, for example, Takasaki et al., *Nature Biotech*

15:1266 (1977). These methods may also be used to investigate the interaction between a targeted protein and peptides selected by phage display or other affinity selection processes, thereby suggesting further modifications of peptides to increase binding affinity and the ability of the peptide to inhibit the activity of the protein.

- 5 In one embodiment, the peptides of the present invention are generated as families of related peptides. Exemplary peptides are represented by SEQ ID NO: 1 through 132. These exemplary peptides were derived through an selection process in which the best binders generated by phage display technology were further analyzed by phage ELISA to obtain candidate peptides by an affinity selection technique such as phage display technology as described herein.
- 10 However, the peptides of the present invention may be produced by any number of known methods including chemical synthesis as described below.

 The peptides of the present invention can be further improved by the process of "affinity maturation". This procedure is directed to increasing the affinity or the activity of the peptides and peptibodies of the present invention using phage display or other selection technologies.

- 15 Based on a consensus sequence, directed secondary phage display libraries, for example, can be generated in which the "core" amino acids (determined from the consensus sequence) are held constant or are biased in frequency of occurrence. Alternatively, an individual peptide sequence can be used to generate a biased, directed phage display library. Panning of such libraries under more stringent conditions can yield peptides with enhanced binding to myostatin, selective
- 20 binding to myostatin, or with some additional desired property. However, peptides having the affinity matured sequences may then be produced by any number of known methods including chemical synthesis or recombinantly. These peptides are used to generate binding agents such as peptibodies of various configurations which exhibit greater inhibitory activity in cell-based assays and *in vivo* assays.

- 25 Example 6 below describes affinity maturation of the "first round" peptides described above to produce affinity matured peptides. Exemplary affinity matured peptibodies are presented in Tables IV and V. The resultant 1x and 2x peptibodies made from these peptides were then further characterized for binding affinity, ability to neutralize myostatin activity, specificity to myostatin as opposed to other TNF β family members, and for additional *in vitro* and *in vivo*
- 30 activity, as described below. Affinity-matured peptides and peptibodies are referred to by the prefix "m" before their family name to distinguish them from first round peptides of the same family.

- Exemplary first round peptides chosen for further affinity maturation according to the present invention included the following peptides: TN8-19 QGHCTRWPWMCPPY (SEQ ID
- 35 NO: 33), and the linear peptides Linear-2 MEMLDSLFECLKDMVPISKA (SEQ ID NO: 104),

Linear-15 HHGWNLYLRKGSAPQWFEEAWV (SEQ ID NO: 117), Linear-17,
RATLLKDFWQLVEGYGDN (SEQ ID NO: 119), Linear-20 YREMSMLEGLLDVLERLQHY
(SEQ ID NO: 122), Linear-21 HNSSQMLLSELIMLVGSMMQ (SEQ ID NO: 123), Linear-24
EFFHWLHNHRSEVNHWLDNM (SEQ ID NO: 126). The affinity matured families of each of
5 these is presented below in Tables IV and V.

The peptides of the present invention also encompass variants and derivatives of the
selected peptides which are capable of binding myostatin. As used herein the term "variant"
refers to peptides having one or more amino acids inserted, deleted, or substituted into the original
amino acid sequence, and which are still capable of binding to myostatin. Insertional and
10 substitutional variants may contain natural amino acids as well as non-naturally occurring amino
acids. As used herein the term "variant" includes fragments of the peptides which still retain the
ability to bind to myostatin. As used herein, the term "derivative" refers to peptides which have
been modified chemically in some manner distinct from insertion, deletion, and substitution
variants. Variants and derivatives of the peptides and peptibodies of the present invention are
15 described more fully below.

Vehicles

As used herein the term "vehicle" refers to a molecule that may be attached to one or
more peptides of the present invention. Preferably, vehicles confer at least one desired property
20 on the binding agents of the present invention. Peptides alone are likely to be removed *in vivo*
either by renal filtration, by cellular clearance mechanisms in the reticuloendothelial system, or by
proteolytic degradation. Attachment to a vehicle improves the therapeutic value of a binding
agent by reducing degradation of the binding agent and/or increasing half-life, reducing toxicity,
reducing immunogenicity, and/or increasing the biological activity of the binding agent.

25 Exemplary vehicles include Fc domains; linear polymers such as polyethylene glycol
(PEG), polylysine, dextran; a branched chain polymer (see for example U.S. Patent No. 4,289,872
to Denkenwalter *et al.*, issued September 15, 1981; U. S. Patent No. 5,229,490 to Tam, issued
July 20, 1993; WO 93/21259 by Frechet *et al.*, published 28 October 1993); a lipid; a cholesterol
group (such as a steroid); a carbohydrate or oligosaccharide; or any natural or synthetic protein,
30 polypeptide or peptide that binds to a salvage receptor.

In one embodiment, the myostatin binding agents of the present invention have at least
one peptide attached to at least one vehicle (F^1 , F^2) through the N-terminus, C-terminus or a side
chain of one of the amino acid residues of the peptide(s). Multiple vehicles may also be used;
such as an Fc domain at each terminus or an Fc domain at a terminus and a PEG group at the
35 other terminus or a side chain.

An Fc domain is one preferred vehicle. As used herein, the term "Fc domain" encompasses native Fc and Fc variant molecules and sequences as defined below. As used herein the term "native Fc" refers to a non-antigen binding fragment of an antibody or the amino acid sequence of that fragment which is produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. A preferred Fc is a fully human Fc and may originate from any of the immunoglobulins, such as IgG1 and IgG2. However, Fc molecules that are partially human, or originate from non-human species are also included herein. Native Fc molecules are made up of monomeric polypeptides that may be linked into dimeric or multimeric forms by covalent (*i.e.*, disulfide bonds) and non-covalent association. The number of intermolecular disulfide bonds between monomeric subunits of native Fc molecules ranges from 1 to 4 depending on class (*e.g.*, IgG, IgA, IgE) or subclass (*e.g.*, IgG1, IgG2, IgG3, IgA1, IgGA2). One example of a native Fc is a disulfide-bonded dimer resulting from papain digestion of an IgG (see Ellison *et al.* (1982), *Nucl Acids Res* 10: 4071-9). The term "native Fc" as used herein is used to refer to the monomeric, dimeric, and multimeric forms.

As used herein, the term "Fc variant" refers to a modified form of a native Fc sequence provided that binding to the salvage receptor is maintained, as described, for example, in WO 97/34631 and WO 96/32478, both of which are incorporated herein by reference. Fc variants may be constructed for example, by substituting or deleting residues, inserting residues or truncating portions containing the site. The inserted or substituted residues may also be altered amino acids, such as peptidomimetics or D-amino acids. Fc variants may be desirable for a number of reasons, several of which are described below. Exemplary Fc variants include molecules and sequences in which:

1. Sites involved in disulfide bond formation are removed. Such removal may avoid reaction with other cysteine-containing proteins present in the host cell used to produce the molecules of the invention. For this purpose, the cysteine-containing segment at the N-terminus may be truncated or cysteine residues may be deleted or substituted with other amino acids (*e.g.*, alanyl, seryl). Even when cysteine residues are removed, the single chain Fc domains can still form a dimeric Fc domain that is held together non-covalently.

2. A native Fc is modified to make it more compatible with a selected host cell. For example, one may remove the PA sequence near the N-terminus of a typical native Fc, which may be recognized by a digestive enzyme in *E. coli* such as proline iminopeptidase. One may also add an N-terminal methionyl residue, especially when the molecule is expressed recombinantly in a bacterial cell such as *E. coli*.

3. A portion of the N-terminus of a native Fc is removed to prevent N-terminal heterogeneity when expressed in a selected host cell. For this purpose, one may delete any of the first 20 amino acid residues at the N-terminus, particularly those at positions 1, 2, 3, 4 and 5.

4. One or more glycosylation sites are removed. Residues that are typically glycosylated (e.g., asparagine) may confer cytolytic response. Such residues may be deleted or substituted with unglycosylated residues (e.g., alanine).

5. Sites involved in interaction with complement, such as the C1q binding site, are removed. For example, one may delete or substitute the EKK sequence of human IgG1. Complement recruitment may not be advantageous for the molecules of this invention and so may be avoided with such an Fc variant.

6. Sites are removed that affect binding to Fc receptors other than a salvage receptor. A native Fc may have sites for interaction with certain white blood cells that are not required for the fusion molecules of the present invention and so may be removed.

7. The ADCC site is removed. ADCC sites are known in the art. See, for example, *Molec Immunol* 29 (5):633-9 (1992) with regard to ADCC sites in IgG1. These sites, as well, are not required for the fusion molecules of the present invention and so may be removed.

8. When the native Fc is derived from a non-human antibody, the native Fc may be humanized. Typically, to humanize a native Fc, one will substitute selected residues in the non-human native Fc with residues that are normally found in human native Fc. Techniques for antibody humanization are well known in the art.

The term "Fc domain" includes molecules in monomeric or multimeric form, whether digested from whole antibody or produced by other means. As used herein the term "multimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two or more polypeptide chains associated covalently, noncovalently, or by both covalent and non-covalent interactions. IgG molecules typically form dimers; IgM, pentamers; IgD, dimers; and IgA, monomers, dimers, trimers, or tetramers. Multimers may be formed by exploiting the sequence and resulting activity of the native Ig source of the Fc or by derivatizing such a native Fc. The term "dimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two polypeptide chains associated covalently or non-covalently.

Additionally, an alternative vehicle according to the present invention is a non-Fc domain protein, polypeptide, peptide, antibody, antibody fragment, or small molecule (e.g., a peptidomimetic compound) capable of binding to a salvage receptor. For example, one could use as a vehicle a polypeptide as described in U.S. Patent No. 5,739,277, issued April 14, 1998 to Presta *et al.* Peptides could also be selected by phage display for binding to the FcRn salvage receptor. Such salvage receptor-binding compounds are also included within the meaning of

“vehicle” and are within the scope of this invention. Such vehicles should be selected for increased half-life (*e.g.*, by avoiding sequences recognized by proteases) and decreased immunogenicity (*e.g.*, by favoring non-immunogenic sequences, as discovered in antibody humanization).

5 In addition, polymer vehicles may also be used to construct the binding agents of the present invention. Various means for attaching chemical moieties useful as vehicles are currently available, see, *e.g.*, Patent Cooperation Treaty (“PCT”) International Publication No. WO 96/11953, entitled “N-Terminally Chemically Modified Protein Compositions and Methods,” herein incorporated by reference in its entirety. This PCT publication discloses, among other
10 things, the selective attachment of water soluble polymers to the N-terminus of proteins.

A preferred polymer vehicle is polyethylene glycol (PEG). The PEG group may be of any convenient molecular weight and may be linear or branched. The average molecular weight of the PEG will preferably range from about 2 kDa to about 100 kDa, more preferably from about 5 kDa to about 50 kDa, most preferably from about 5 kDa to about 10 kDa. The PEG groups will
15 generally be attached to the compounds of the invention via acylation or reductive alkylation through a reactive group on the PEG moiety (*e.g.*, an aldehyde, amino, thiol, or ester group) to a reactive group on the inventive compound (*e.g.*, an aldehyde, amino, or ester group). A useful strategy for the PEGylation of synthetic peptides consists of combining, through forming a conjugate linkage in solution, a peptide and a PEG moiety, each bearing a special functionality
20 that is mutually reactive toward the other. The peptides can be easily prepared with conventional solid phase synthesis as known in the art. The peptides are “preactivated” with an appropriate functional group at a specific site. The precursors are purified and fully characterized prior to reacting with the PEG moiety. Ligation of the peptide with PEG usually takes place in aqueous phase and can be easily monitored by reverse phase analytical HPLC. The PEGylated peptides
25 can be easily purified by preparative HPLC and characterized by analytical HPLC, amino acid analysis and laser desorption mass spectrometry.

Polysaccharide polymers are another type of water soluble polymer which may be used for protein modification. Dextran is polysaccharide polymers comprised of individual subunits of glucose predominantly linked by α 1-6 linkages. The dextran itself is available in many
30 molecular weight ranges, and is readily available in molecular weights from about 1 kDa to about 70 kDa. Dextran is a suitable water-soluble polymer for use in the present invention as a vehicle by itself or in combination with another vehicle (*e.g.*, Fc). See, for example, WO 96/11953 and WO 96/05309. The use of dextran conjugated to therapeutic or diagnostic immunoglobulins has been reported; see, for example, European Patent Publication No. 0 315 456, which is hereby

incorporated by reference. Dextran of about 1 kDa to about 20 kDa is preferred when dextran is used as a vehicle in accordance with the present invention.

Linkers

5 The binding agents of the present invention may optionally further comprise a "linker" group. Linkers serve primarily as a spacer between a peptide and a vehicles or between two peptides of the binding agents of the present invention. In one embodiment, the linker is made up of amino acids linked together by peptide bonds, preferably from 1 to 20 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally occurring amino acids.
10 One or more of these amino acids may be glycosylated, as is understood by those in the art. In one embodiment, the 1 to 20 amino acids are selected from glycine, alanine, proline, asparagine, glutamine, and lysine. Preferably, a linker is made up of a majority of amino acids that are sterically unhindered, such as glycine and alanine. Thus, exemplary linkers are polyglycines (particularly (Gly)₅, (Gly)₈), poly(Gly-Ala), and polyalanines. As used herein, the designation
15 "g" refers to a glycine homopeptide linkers. As shown in Table II, "gn" refers to a 5x gly linker at the N terminus, while "gc" refers to 5x gly linker at the C terminus. Combinations of Gly and Ala are also preferred. One exemplary linker sequence useful for constructing the binding agents of the present invention is the following: gsgsatggsgstassgsgsatg (Seq ID No: 305). This linker sequence is referred to as the "k" or 1k sequence. The designations "kc", as found in Table II,
20 refers to the k linker at the C-terminus, while the designation "kn", refers to the k linker at the N-terminus.

 The linkers of the present invention may also be non-peptide linkers. For example, alkyl linkers such as -NH-(CH₂)_s-C(O)-, wherein s = 2-20 can be used. These alkyl linkers may further be substituted by any non-sterically hindering group such as lower alkyl (e.g., C₁-C₆) lower acyl,
25 halogen (e.g., Cl, Br), CN, NH₂, phenyl, etc. An exemplary non-peptide linker is a PEG linker, and has a molecular weight of 100 to 5000 kDa, preferably 100 to 500 kDa. The peptide linkers may be altered to form derivatives in the same manner as above.

Exemplary Binding Agents

30 The binding agents of the present invention comprise at least one peptide capable of binding myostatin. In one embodiment, the myostatin binding peptide is between about 5 and about 50 amino acids in length, in another, between about 10 and 30 amino acids in length, and in another, between about 10 and 25 amino acids in length. In one embodiment the myostatin binding peptide comprises the amino acid sequence WMCPP (SEQ ID NO: 633). In other
35 embodiment, the myostatin binding peptide comprises the amino acid sequence

C_{a1}a₂Wa₃WMCPP (SEQ ID NO: 352), wherein a₁, a₂ and a₃ are selected from a neutral hydrophobic, neutral polar, or basic amino acid. In another embodiment the myostatin binding peptide comprises the amino acid sequence Cb₁b₂Wb₃WMCPP (SEQ ID NO: 353), wherein b₁ is selected from any one of the amino acids T, I, or R; b₂ is selected from any one of R, S, Q; b₃ is selected from any one of P, R and Q, and wherein the peptide is between 10 and 50 amino acids in length, and physiologically acceptable salts thereof.

In another embodiment, the myostatin binding peptide comprises the formula:

c₁c₂c₃c₄c₅c₆Cc₇c₈Wc₉WMCPPc₁₀c₁₁c₁₂c₁₃ (SEQ ID NO: 354), wherein:

c₁ is absent or any amino acid;

c₂ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

c₃ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

c₄ is absent or any amino acid;

c₅ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

c₆ is absent or a neutral hydrophobic, neutral polar, or basic amino acid;

c₇ is a neutral hydrophobic, neutral polar, or basic amino acid;

c₈ is a neutral hydrophobic, neutral polar, or basic amino acid;

c₉ is a neutral hydrophobic, neutral polar or basic amino acid; and

c₁₀ to c₁₃ is any amino acid; and wherein the peptide is between 20 and 50 amino acids in

length, and physiologically acceptable salts thereof.

A related embodiment the myostatin binding peptide comprises the formula:

d₁d₂d₃d₄d₅d₆Cd₇d₈Wd₉WMCPPd₁₀d₁₁d₁₂d₁₃ (SEQ ID NO: 355), wherein

d₁ is absent or any amino acid;

d₂ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

d₃ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

d₄ is absent or any amino acid;

d₅ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

d₆ is absent or a neutral hydrophobic, neutral polar, or basic amino acid;

d₇ is selected from any one of the amino acids T, I, or R;

d₈ is selected from any one of R, S, Q;

d₉ is selected from any one of P, R and Q, and

d₁₀ to d₁₃ is selected from any amino acid,

and wherein the peptide is between 20 and 50 amino acids in length, and physiologically acceptable salts thereof.

Additional embodiments of binding agents comprise at least one of the following peptides:

(1) a peptide capable of binding myostatin, wherein the peptide comprises the sequence

WYe₁e₂Ye₃G, (SEQ ID NO: 356)

wherein e₁ is P, S or Y,

e₂ is C or Q, and

e_3 is G or H, wherein the peptide is between 7 and 50 amino acids in length, and physiologically acceptable salts thereof.

(2) a peptide capable of binding myostatin, wherein the peptide comprises the sequence $f_1EMLf_2SLf_3f_4LL$, (SEQ ID NO: 455),

5 wherein f_1 is M or I,
 f_2 is any amino acid,
 f_3 is L or F,
 f_4 is E, Q or D;
 and wherein the peptide is between 7 and 50 amino acids in length, and physiologically
 10 acceptable salts thereof.

(3) a peptide capable of binding myostatin wherein the peptide comprises the sequence $Lg_1g_2LLg_3g_4L$, (SEQ ID NO: 456), wherein

g_1 is Q, D or E,
 g_2 is S, Q, D or E,
 15 g_3 is any amino acid,
 g_4 is L, W, F, or Y, and wherein the peptide is between 8 and 50 amino acids in length,
 and physiologically acceptable salts thereof.

(4) a peptide capable of binding myostatin, wherein the peptide comprises the sequence $h_1h_2h_3h_4h_5h_6h_7h_8h_9$ (SEQ ID NO: 457), wherein

20 h_1 is R or D,
 h_2 is any amino acid,
 h_3 is A, T S or Q,
 h_4 is L or M,
 h_5 is L or S,
 25 h_6 is any amino acid,
 h_7 is F or E,
 h_8 is W, F or C,
 h_9 is L, F, M or K, and wherein the peptide is between 9 and 50 amino acids in length,
 and physiologically acceptable salts thereof.

30 In one embodiment, the binding agents of the present invention further comprise at least one vehicle such as a polymer or an Fc domain, and may further comprise at least one linker sequence. In this embodiment, the binding agents of the present invention are constructed so that at least one myostatin-binding peptide is covalently attached to at least one vehicle. The peptide or peptides are attached directly or indirectly through a linker sequence, to the vehicle at the N-
 35 terminal, C-terminal or an amino acid sidechain of the peptide. In this embodiment, the binding agents of the present invention have the following generalized structure:

$(X^1)_a-F^1-(X^2)_b$, or multimers thereof;

wherein F^1 is a vehicle; and X^1 and X^2 are each independently selected from

$-(L^1)_c-P^1$;

40 $-(L^1)_c-P^1-(L^2)_d-P^2$;

$-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$;

and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$;

wherein P^1 , P^2 , P^3 , and P^4 are peptides capable of binding myostatin; and

L^1 , L^2 , L^3 , and L^4 are each linkers; and a, b, c, d, e, and f are each independently 0 or 1,

provided that at least one of a and b is 1.

In one embodiment of the binding agents having this generalized structure, the peptides P^1 , P^2 , P^3 , and P^4 can be selected from one or more of any of the peptides comprising the sequences provided above. Peptides P^1 , P^2 , P^3 , and P^4 can be selected from one or more peptides comprising any of the following sequences: SEQ ID NO: 633, SEQ ID NO: 352, SEQ ID NO: 353, SEQ ID NO: 354, SEQ ID NO: 355, SEQ ID NO: 356, SEQ ID NO: 455, SEQ ID NO: 456, or SEQ ID NO: 457.

In a further embodiment, the vehicles of binding agents having the general formula above are Fc domains. The peptides are therefore fused to an Fc domain, either directly or indirectly, thereby providing peptibodies. The peptibodies of the present invention display a high binding affinity for myostatin and can inhibit the activity of myostatin as demonstrated by *in vitro* assays and *in vivo* testing in animals provided herein.

The present invention also provides nucleic acid molecules comprising polynucleotides encoding the peptides, peptibodies, and peptide and peptibody variants and derivatives of the present invention. Exemplary nucleotides sequences are given below.

20 Variants and Derivatives of Peptides and Peptibodies

The binding agents of the present invention also encompass variants and derivatives of the peptides and peptibodies described herein. Since both the peptides and peptibodies of the present invention can be described in terms of their amino acid sequence, the terms "variants" and "derivatives" can be said to apply to a peptide alone, or a peptide as a component of a peptibody. As used herein, the term "peptide variants" refers to peptides or peptibodies having one or more amino acid residues inserted, deleted or substituted into the original amino acid sequence and which retain the ability to bind to myostatin and modify its activity. As used herein, fragments of the peptides or peptibodies are included within the definition of "variants".

It is understood that any given peptide or peptibody may contain one or two or all three types of variants. Insertional and substitutional variants may contain natural amino acids, as well as non-naturally occurring amino acids or both.

Peptide and peptibody variants also include mature peptides and peptibodies wherein leader or signal sequences are removed, and the resulting proteins having additional amino terminal residues, which amino acids may be natural or non-natural. Peptibodies with an

additional methionyl residue at amino acid position -1 (Met⁻¹-peptibody) are contemplated, as are peptibodies with additional methionine and lysine residues at positions -2 and -1 (Met⁻²-Lys⁻¹-). Variants having additional Met, Met-Lys, Lys residues (or one or more basic residues, in general) are particularly useful for enhanced recombinant protein production in bacterial host cells.

5 Peptide or peptibody variants of the present invention also includes peptides having additional amino acid residues that arise from use of specific expression systems. For example, use of commercially available vectors that express a desired polypeptide as part of glutathione-S-transferase (GST) fusion product provides the desired polypeptide having an additional glycine residue at amino acid position-1 after cleavage of the GST component from the desired
10 polypeptide. Variants which result from expression in other vector systems are also contemplated, including those wherein histidine tags are incorporated into the amino acid sequence, generally at the carboxy and/or amino terminus of the sequence.

 In one example, insertional variants are provided wherein one or more amino acid residues, either naturally occurring or non-naturally occurring amino acids, are added to a peptide
15 amino acid sequence. Insertions may be located at either or both termini of the protein, or may be positioned within internal regions of the peptibody amino acid sequence. Insertional variants with additional residues at either or both termini can include, for example, fusion proteins and proteins including amino acid tags or labels. Insertional variants include peptides in which one or more amino acid residues are added to the peptide amino acid sequence or fragment thereof.

20 Insertional variants also include fusion proteins wherein the amino and/or carboxy termini of the peptide or peptibody is fused to another polypeptide, a fragment thereof or amino acids which are not generally recognized to be part of any specific protein sequence. Examples of such fusion proteins are immunogenic polypeptides, proteins with long circulating half lives, such as immunoglobulin constant regions, marker proteins, proteins or polypeptides that facilitate
25 purification of the desired peptide or peptibody, and polypeptide sequences that promote formation of multimeric proteins (such as leucine zipper motifs that are useful in dimer formation/stability).

 This type of insertional variant generally has all or a substantial portion of the native molecule, linked at the N- or C-terminus, to all or a portion of a second polypeptide. For
30 example, fusion proteins typically employ leader sequences from other species to permit the recombinant expression of a protein in a heterologous host. Another useful fusion protein includes the addition of an immunologically active domain, such as an antibody epitope, to facilitate purification of the fusion protein. Inclusion of a cleavage site at or near the fusion junction will facilitate removal of the extraneous polypeptide after purification. Other useful

fusions include linking of functional domains, such as active sites from enzymes, glycosylation domains, cellular targeting signals or transmembrane regions.

There are various commercially available fusion protein expression systems that may be used in the present invention. Particularly useful systems include but are not limited to the
5 glutathione-S-transferase (GST) system (Pharmacia), the maltose binding protein system (NEB, Beverley, MA), the FLAG system (IBI, New Haven, CT), and the 6xHis system (Qiagen, Chatsworth, CA). These systems are capable of producing recombinant peptides and/or peptibodies bearing only a small number of additional amino acids, which are unlikely to significantly affect the activity of the peptide or peptibody. For example, both the FLAG system
10 and the 6xHis system add only short sequences, both of which are known to be poorly antigenic and which do not adversely affect folding of a polypeptide to its native conformation. Another N-terminal fusion that is contemplated to be useful is the fusion of a Met-Lys dipeptide at the N-terminal region of the protein or peptides. Such a fusion may produce beneficial increases in protein expression or activity.

15 Other fusion systems produce polypeptide hybrids where it is desirable to excise the fusion partner from the desired peptide or peptibody. In one embodiment, the fusion partner is linked to the recombinant peptibody by a peptide sequence containing a specific recognition sequence for a protease. Examples of suitable sequences are those recognized by the Tobacco Etch Virus protease (Life Technologies, Gaithersburg, MD) or Factor Xa (New England Biolabs,
20 Beverley, MA).

The invention also provides fusion polypeptides which comprise all or part of a peptide or peptibody of the present invention, in combination with truncated tissue factor (tTF). tTF is a vascular targeting agent consisting of a truncated form of a human coagulation-inducing protein that acts as a tumor blood vessel clotting agent, as described U.S. Patent Nos.: 5,877,289;
25 6,004,555; 6,132,729; 6,132,730; 6,156,321; and European Patent No. EP 0988056. The fusion of tTF to the anti-myostatin peptibody or peptide, or fragments thereof facilitates the delivery of anti-myostatin antagonists to target cells, for example, skeletal muscle cells, cardiac muscle cells, fibroblasts, pre-adipocytes, and possibly adipocytes.

In another aspect, the invention provides deletion variants wherein one or more amino
30 acid residues in a peptide or peptibody are removed. Deletions can be effected at one or both termini of the peptibody, or from removal of one or more residues within the peptibody amino acid sequence. Deletion variants necessarily include all fragments of a peptide or peptibody.

In still another aspect, the invention provides substitution variants of peptides and peptibodies of the invention. Substitution variants include those peptides and peptibodies wherein
35 one or more amino acid residues are removed and replaced with one or more alternative amino

acids, which amino acids may be naturally occurring or non-naturally occurring. Substitutional variants generate peptides or peptibodies that are "similar" to the original peptide or peptibody, in that the two molecules have a certain percentage of amino acids that are identical. Substitution variants include substitutions of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, and 20 amino acids within a peptide or peptibody, wherein the number of substitutions may be up to ten percent of the amino acids of the peptide or peptibody. In one aspect, the substitutions are conservative in nature, however, the invention embraces substitutions that are also non-conservative and also includes unconventional amino acids.

Identity and similarity of related peptides and peptibodies can be readily calculated by known methods. Such methods include, but are not limited to, those described in Computational Molecular Biology, Lesk, A.M., ed., Oxford University Press, New York (1988); Biocomputing: Informatics and Genome Projects, Smith, D.W., ed., Academic Press, New York (1993); Computer Analysis of Sequence Data, Part 1, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey (1994); Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press (1987); Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M. Stockton Press, New York (1991); and Carillo *et al.*, *SIAM J. Applied Math.*, 48:1073 (1988).

Preferred methods to determine the relatedness or percent identity of two peptides or polypeptides, or a polypeptide and a peptide, are designed to give the largest match between the sequences tested. Methods to determine identity are described in publicly available computer programs. Preferred computer program methods to determine identity between two sequences include, but are not limited to, the GCG program package, including GAP (Devereux *et al.*, *Nucl. Acid. Res.*, 12:387 (1984); Genetics Computer Group, University of Wisconsin, Madison, WI, BLASTP, BLASTN, and FASTA (Altschul *et al.*, *J. Mol. Biol.*, 215:403-410 (1990)). The BLASTX program is publicly available from the National Center for Biotechnology Information (NCBI) and other sources (*BLAST Manual*, Altschul *et al.* NCB/NLM/NIH Bethesda, MD 20894; Altschul *et al.*, *supra* (1990)). The well-known Smith Waterman algorithm may also be used to determine identity.

Certain alignment schemes for aligning two amino acid sequences may result in the matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, in certain embodiments, the selected alignment method will result in an alignment that spans at least ten percent of the full length of the target polypeptide being compared, *i.e.*, at least 40 contiguous amino acids where sequences of at least 400 amino acids are being compared, 30 contiguous amino acids where sequences of at least 300 to about 400 amino

acids are being compared, at least 20 contiguous amino acids where sequences of 200 to about 300 amino acids are being compared, and at least 10 contiguous amino acids where sequences of about 100 to 200 amino acids are being compared. For example, using the computer algorithm GAP (Genetics Computer Group, University of Wisconsin, Madison, WI), two polypeptides for which the percent sequence identity is to be determined are aligned for optimal matching of their respective amino acids (the "matched span", as determined by the algorithm). In certain embodiments, a gap opening penalty (which is typically calculated as 3X the average diagonal; the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix (see Dayhoff *et al.*, *Atlas of Protein Sequence and Structure*, 5(3)(1978) for the PAM 250 comparison matrix; Henikoff *et al.*, *Proc. Natl. Acad. Sci USA*, 89:10915-10919 (1992) for the BLOSUM 62 comparison matrix) is also used by the algorithm.

In certain embodiments, for example, the parameters for a polypeptide sequence comparison can be made with the following: Algorithm: Needleman *et al.*, *J. Mol. Biol.*, 48:443-453 (1970); Comparison matrix: BLOSUM 62 from Henikoff *et al.*, *supra* (1992); Gap Penalty: 12; Gap Length Penalty: 4; Threshold of Similarity: 0, along with no penalty for end gaps.

In certain embodiments, the parameters for polynucleotide molecule sequence (as opposed to an amino acid sequence) comparisons can be made with the following: Algorithm: Needleman *et al.*, *supra* (1970); Comparison matrix: matches = +10, mismatch = 0; Gap Penalty: 50; Gap Length Penalty: 3

Other exemplary algorithms, gap opening penalties, gap extension penalties, comparison matrices, thresholds of similarity, etc. may be used, including those set forth in the Program Manual, Wisconsin Package, Version 9, September, 1997. The particular choices to be made will be apparent to those of skill in the art and will depend on the specific comparison to be made, such as DNA-to-DNA, protein-to-protein, protein-to-DNA; and additionally, whether the comparison is between given pairs of sequences (in which case GAP or BestFit are generally preferred) or between one sequence and a large database of sequences (in which case FASTA or BLASTA are preferred).

Stereoisomers (*e.g.*, D-amino acids) of the twenty conventional (naturally occurring) amino acids, non-naturally occurring amino acids such as α -, α -disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components

for peptides of the present invention. Examples of non-naturally occurring amino acids include, for example: aminoadipic acid, beta-alanine, beta-aminopropionic acid, aminobutyric acid, piperidinic acid, aminocaproic acid, aminoheptanoic acid, aminoisobutyric acid, aminopimelic acid, diaminobutyric acid, desmosine, diaminopimelic acid, diaminopropionic acid, N-ethylglycine, N-ethylasparagine, hydroxylysine, all-0-hydroxylysine, hydroxyproline, isodesmosine, allo-isoleucine, N-methylglycine, sarcosine, N-methylisoleucine, N-methylvaline, norvaline, norleucine, orithine, 4-hydroxyproline, γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ -N-methylarginine, and other similar amino acids and amino acids (*e.g.*, 4-hydroxyproline).

Naturally occurring residues may be divided into (overlapping) classes based on common side chain properties:

- 1) neutral hydrophobic: Met, Ala, Val, Leu, Ile, Pro, Trp, Met, Phe;
- 2) neutral polar: Cys, Ser, Thr, Asn, Gln, Tyr, Gly;
- 3) acidic: Asp, Glu;
- 4) basic: His, Lys, Arg;
- 5) residues that influence chain orientation: Gly, Pro; and
- 6) aromatic: Trp, Tyr, Phe.

Substitutions of amino acids may be conservative, which produces peptides having functional and chemical characteristics similar to those of the original peptide. Conservative amino acid substitutions involve exchanging a member of one of the above classes for another member of the same class. Conservative changes may encompass unconventional amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties.

Non-conservative substitutions may involve the exchange of a member of one of these classes for a member from another class. These changes can result in substantial modification in the functional and/or chemical characteristics of the peptides. In making such changes, according to certain embodiments, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine

(-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte *et al.*, *J. Mol. Biol.*, 157:105-131 (1982). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in certain embodiments, the substitution of amino acids whose hydropathic indices are within ± 2 is included. In certain embodiments, those which are within ± 1 are included, and in certain embodiments, those within ± 0.5 are included.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional peptidobody or peptide thereby created is intended for use in immunological embodiments, as in the present case. In certain embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigenicity, *i.e.*, with a biological property of the protein.

The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 \pm 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5) and tryptophan (-3.4). In making changes based upon similar hydrophilicity values, in certain embodiments, the substitution of amino acids whose hydrophilicity values are within ± 2 is included, in certain embodiments, those which are within ± 1 are included, and in certain embodiments, those within ± 0.5 are included. One may also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

Exemplary amino acid substitutions are set forth in Table 1 below.

| <u>Amino Acid Substitutions</u> | | |
|---------------------------------|-------------------------|-------------------------|
| Original Residues | Exemplary Substitutions | Preferred Substitutions |
| Ala | Val, Leu, Ile | Val |
| Arg | Lys, Gln, Asn | Lys |
| Asn | Gln, Glu, Asp | Gln |
| Asp | Glu, Gln, Asp | Glu |
| Cys | Ser, Ala | Ser |

| | | |
|-----|---|-----|
| Gln | Asn, Glu, Asp | Asn |
| Glu | Asp, Gln, Asn | Asp |
| Gly | Pro, Ala | Ala |
| His | Asn, Gln, Lys, Arg | Arg |
| Ile | Leu, Val, Met, Ala, Phe, Norleucine | Leu |
| Leu | Norleucine, Ile, Val, Met, Ala, Phe | Ile |
| Lys | Arg, 1,4 Diamino-butyric Acid, Gln, Asn | Arg |
| Met | Leu, Phe, Ile | Leu |
| Phe | Leu, Val, Ile, Ala, Tyr | Leu |
| Pro | Ala | Gly |
| Ser | Thr, Ala, Cys | Thr |
| Thr | Ser | Ser |
| Trp | Tyr, Phe | Tyr |
| Tyr | Trp, Phe, Thr, Ser | Phe |
| Val | Ile, Met, Leu, Phe, Ala, Norleucine | Leu |

One skilled in the art will be able to produce variants of the peptides and peptibodies of the present invention by random substitution, for example, and testing the resulting peptide or peptibody for binding activity using the assays described herein.

- 5 Additionally, one skilled in the art can review structure-function studies or three-dimensional structural analysis in order to identify residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues which are important for activity or structure in similar proteins. One skilled in the art may opt for chemically similar
- 10 amino acid substitutions for such predicted important amino acid residues. The variants can then be screened using activity assays as described herein.

- A number of scientific publications have been devoted to the prediction of secondary structure. See Moult J., *Curr. Op. in Biotech.*, 7(4):422-427 (1996), Chou *et al.*, *Biochemistry*, 13(2):222-245 (1974); Chou *et al.*, *Biochemistry*, 113(2):211-222 (1974); Chou *et al.*, *Adv.*
- 15 *Enzymol. Relat. Areas Mol. Biol.*, 47:45-148 (1978); Chou *et al.*, *Ann. Rev. Biochem.*, 47:251-276 and Chou *et al.*, *Biophys. J.*, 26:367-384 (1979). Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins which

have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a protein's structure. See Holm *et al.*, *Nucl. Acid. Res.*, 27(1):244-247 (1999). It has been
5 suggested (Brenner *et al.*, *Curr. Op. Struct. Biol.*, 7(3):369-376 (1997)) that there are a limited number of folds in a given protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate.

Additional methods of predicting secondary structure include "threading" (Jones, D., *Curr. Opin. Struct. Biol.*, 7(3):377-87 (1997); Sippl *et al.*, *Structure*, 4(1):15-19 (1996)), "profile
10 analysis" (Bowie *et al.*, *Science*, 253:164-170 (1991); Gribskov *et al.*, *Meth. Enzym.*, 183:146-159 (1990); Gribskov *et al.*, *Proc. Nat. Acad. Sci.*, 84(13):4355-4358 (1987)), and "evolutionary linkage" (See Holm, *supra* (1999), and Brenner, *supra* (1997)).

In certain embodiments, peptide or peptibody variants include glycosylation variants wherein one or more glycosylation sites such as a N-linked glycosylation site, has been added to
15 the peptibody. An N-linked glycosylation site is characterized by the sequence: Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X may be any amino acid residue except proline. The substitution or addition of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions which eliminate this sequence will remove an existing N-linked carbohydrate chain.
20 Also provided is a rearrangement of N-linked carbohydrate chains wherein one or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created.

The invention also provides "derivatives" of the peptides or peptibodies of the present invention. As used herein the term "derivative" refers to modifications other than, or in addition
25 to, insertions, deletions, or substitutions of amino acid residues which retain the ability to bind to myostatin.

Preferably, the modifications made to the peptides of the present invention to produce derivatives are covalent in nature, and include for example, chemical bonding with polymers, lipids, other organic, and inorganic moieties. Derivatives of the invention may be prepared to
30 increase circulating half-life of a peptibody, or may be designed to improve targeting capacity for the peptibody to desired cells, tissues, or organs.

The invention further embraces derivative binding agents covalently modified to include one or more water soluble polymer attachments, such as polyethylene glycol, polyoxyethylene

glycol, or polypropylene glycol, as described U.S. Patent Nos.: 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; and 4,179,337. Still other useful polymers known in the art include monomethoxy-polyethylene glycol, dextran, cellulose, or other carbohydrate based polymers, poly-(N-vinyl pyrrolidone)-polyethylene glycol, propylene glycol homopolymers, a
 5 polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (*e.g.*, glycerol) and polyvinyl alcohol, as well as mixtures of these polymers. Particularly preferred are peptibodies covalently modified with polyethylene glycol (PEG) subunits. Water-soluble polymers may be bonded at specific positions, for example at the amino terminus of the peptibodies, or randomly attached to one or more side chains of the polypeptide. The use of PEG for improving the
 10 therapeutic capacity for binding agents, *e.g.* peptibodies, and for humanized antibodies in particular, is described in US Patent No. 6, 133, 426 to Gonzales *et al.*, issued October 17, 2000.

The invention also contemplates derivatizing the peptide and/or vehicle portion of the myostatin binding agents. Such derivatives may improve the solubility, absorption, biological half-life, and the like of the compounds. The moieties may alternatively eliminate or attenuate
 15 any undesirable side-effect of the compounds and the like. Exemplary derivatives include compounds in which:

1. The derivative or some portion thereof is cyclic. For example, the peptide portion may be modified to contain two or more Cys residues (*e.g.*, in the linker), which could cyclize by disulfide bond formation.
- 20 2. The derivative is cross-linked or is rendered capable of cross-linking between molecules. For example, the peptide portion may be modified to contain one Cys residue and thereby be able to form an intermolecular disulfide bond with a like molecule. The derivative may also be cross-linked through its C-terminus.
3. One or more peptidyl [-C(O)NR-] linkages (bonds) is replaced by a non-peptidyl
 25 linkage. Exemplary non-peptidyl linkages are -CH₂-carbamate [-CH₂-OC(O)NR-], phosphonate, -CH₂-sulfonamide [-CH₂-S(O)₂NR-], urea [-NHC(O)NH-], -CH₂-secondary amine, and alkylated peptide [-C(O)NR₆- wherein R₆ is lower alkyl].
4. The N-terminus is derivatized. Typically, the N-terminus may be acylated or modified to a substituted amine. Exemplary N-terminal derivative groups include -NRR₁ (other than -NH₂),
 30 -NRC(O)R₁, -NRC(O)OR₁, -NRS(O)₂R₁, -NHC(O)NHR₁, succinimide, or benzyloxycarbonyl-NH- (CBZ-NH-), wherein R and R₁ are each independently hydrogen or lower alkyl and wherein the phenyl ring may be substituted with 1 to 3 substituents selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, chloro, and bromo.
5. The free C-terminus is derivatized. Typically, the C-terminus is esterified or amidated.
 35 For example, one may use methods described in the art to add (NH-CH₂-CH₂-NH₂)₂ to

compounds of this invention at the C-terminus. Likewise, one may use methods described in the art to add -NH₂, (or "capping" with an -NH₂ group) to compounds of this invention at the C-terminus. Exemplary C-terminal derivative groups include, for example, -C(O)R₂ wherein R₂ is lower alkoxy or -NR₃R₄ wherein R₃ and R₄ are independently hydrogen or C₁-C₈ alkyl (preferably C₁-C₄ alkyl).

6. A disulfide bond is replaced with another, preferably more stable, cross-linking moiety (e.g., an alkylene). See, e.g., Bhatnagar *et al.*, *J Med Chem* 39: 3814-9 (1996), Alberts *et al.*, *Thirteenth Am Pep Symp*, 357-9 (1993).

7. One or more individual amino acid residues is modified. Various derivatizing agents are known to react specifically with selected side chains or terminal residues, as described in detail below.

Lysiny residues and amino terminal residues may be reacted with succinic or other carboxylic acid anhydrides, which reverse the charge of the lysiny residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimide; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginy residues may be modified by reaction with any one or combination of several conventional reagents, including phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginy residues requires that the reaction be performed in alkaline conditions because of the high pK_a of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

Specific modification of tyrosyl residues has been studied extensively, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidazole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

Carboxyl side chain groups (aspartyl or glutamyl) may be selectively modified by reaction with carbodiimides (R'-N=C=N-R') such as 1-cyclohexyl-3-(2-morpholinyl)-(4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues may be converted to asparaginy and glutaminy residues by reaction with ammonium ions.

Glutaminy and asparaginy residues may be deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues falls within the scope of this invention.

Cysteiny residues can be replaced by amino acid residues or other moieties either to eliminate disulfide bonding or, conversely, to stabilize cross-linking. See, *e.g.*, Bhatnagar et al., (*supra*).

Derivatization with bifunctional agents is useful for cross-linking the peptides or their functional derivatives to a water-insoluble support matrix or to other macromolecular vehicles. Commonly used cross-linking agents include, *e.g.*, 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimide yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Patent Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

Carbohydrate (oligosaccharide) groups may conveniently be attached to sites that are known to be glycosylation sites in proteins. Generally, O-linked oligosaccharides are attached to serine (Ser) or threonine (Thr) residues while N-linked oligosaccharides are attached to asparagine (Asn) residues when they are part of the sequence Asn-X-Ser/Thr, where X can be any amino acid except proline. X is preferably one of the 19 naturally occurring amino acids other than proline. The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each type are different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-linked oligosaccharides and, by virtue of its negative charge, may confer acidic properties to the glycosylated compound. Such site(s) may be incorporated in the linker of the compounds of this invention and are preferably glycosylated by a cell during recombinant production of the polypeptide compounds (*e.g.*, in mammalian cells such as CHO, BHK, COS). However, such sites may further be glycosylated by synthetic or semi-synthetic procedures known in the art.

Other possible modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, oxidation of the sulfur atom in Cys, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains [see, for example, Creighton, *Proteins: Structure and Molecule Properties* (W. H. Freeman & Co., San Francisco), pp. 79-86 (1983)].

Compounds of the present invention may be changed at the DNA level, as well. The DNA sequence of any portion of the compound may be changed to codons more compatible with the

chosen host cell. For *E. coli*, which is the preferred host cell, optimized codons are known in the art. Codons may be substituted to eliminate restriction sites or to include silent restriction sites, which may aid in processing of the DNA in the selected host cell. The vehicle, linker and peptide DNA sequences may be modified to include any of the foregoing sequence changes.

5 Additional derivatives include non-peptide analogs that provide a stabilized structure or lessened biodegradation, are also contemplated. Peptide mimetic analogs can be prepared based on a selected inhibitory peptide by replacement of one or more residues by nonpeptide moieties. Preferably, the nonpeptide moieties permit the peptide to retain its natural confirmation, or stabilize a preferred, *e.g.*, bioactive, confirmation which retains the ability to recognize and bind
10 myostatin. In one aspect, the resulting analog/mimetic exhibits increased binding affinity for myostatin. One example of methods for preparation of nonpeptide mimetic analogs from peptides is described in Nachman *et al.*, *Regul Pept* 57:359-370 (1995). If desired, the peptides of the invention can be modified, for instance, by glycosylation, amidation, carboxylation, or phosphorylation, or by the creation of acid addition salts, amides, esters, in particular C-terminal
15 esters, and N-acyl derivatives of the peptides of the invention. The peptibodies also can be modified to create peptide derivatives by forming covalent or noncovalent complexes with other moieties. Covalently-bound complexes can be prepared by linking the chemical moieties to functional groups on the side chains of amino acids comprising the peptibodies, or at the N- or C-terminus.

20 In particular, it is anticipated that the peptides can be conjugated to a reporter group, including, but not limited to a radiolabel, a fluorescent label, an enzyme (*e.g.*, that catalyzes a colorimetric or fluorometric reaction), a substrate, a solid matrix, or a carrier (*e.g.*, biotin or avidin). The invention accordingly provides a molecule comprising a peptibody molecule, wherein the molecule preferably further comprises a reporter group selected from the group
25 consisting of a radiolabel, a fluorescent label, an enzyme, a substrate, a solid matrix, and a carrier. Such labels are well known to those of skill in the art, *e.g.*, biotin labels are particularly contemplated. The use of such labels is well known to those of skill in the art and is described in, *e.g.*, U.S. Patent Nos. 3,817,837; 3,850,752; 3,996,345; and 4,277,437. Other labels that will be useful include but are not limited to radioactive labels, fluorescent labels and chemiluminescent
30 labels. U.S. Patents concerning use of such labels include, for example, U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; and 3,996,345. Any of the peptibodies of the present invention may comprise one, two, or more of any of these labels.

Methods of Making Peptides and Peptibodies

The peptides of the present invention can be generated using a wide variety of techniques known in the art. For example, such peptides can be synthesized in solution or on a solid support in accordance with conventional techniques. Various automatic synthesizers are commercially available and can be used in accordance with known protocols. See, for example, Stewart and
5 Young (*supra*); Tam *et al.*, *J Am Chem Soc.*, **105**:6442, (1983); Merrifield, *Science* **232**:341-347 (1986); Barany and Merrifield, *The Peptides*, Gross and Meienhofer, eds, Academic Press, New York, 1-284; Barany *et al.*, *Int J Pep Protein Res.*, **30**:705-739 (1987); and U.S. Patent No. 5,424,398, each incorporated herein by reference.

Solid phase peptide synthesis methods use a copoly(styrene-divinylbenzene) containing
10 0.1-1.0 mM amines/g polymer. These methods for peptide synthesis use butyloxycarbonyl (t-BOC) or 9-fluorenylmethyloxy-carbonyl(FMOC) protection of alpha-amino groups. Both methods involve stepwise syntheses whereby a single amino acid is added at each step starting from the C-terminus of the peptide (See, Coligan *et al.*, *Curr Prot Immunol*, Wiley Interscience, 1991, Unit 9). On completion of chemical synthesis, the synthetic peptide can be deprotected to
15 remove the t-BOC or FMOC amino acid blocking groups and cleaved from the polymer by treatment with acid at reduced temperature (*e.g.*, liquid HF-10% anisole for about 0.25 to about 1 hours at 0°C). After evaporation of the reagents, the peptides are extracted from the polymer with 1% acetic acid solution that is then lyophilized to yield the crude material. This can normally be purified by such techniques as gel filtration on Sephadex G-15 using 5% acetic acid as a solvent.
20 Lyophilization of appropriate fractions of the column will yield the homogeneous peptides or peptide derivatives, which can then be characterized by such standard techniques as amino acid analysis, thin layer chromatography, high performance liquid chromatography, ultraviolet absorption spectroscopy, molar rotation, solubility, and quantitated by the solid phase Edman degradation.

25 Phage display techniques can be particularly effective in identifying the peptides of the present invention as described above. Briefly, a phage library is prepared (using *e.g.* ml 13, fd, or lambda phage), displaying inserts from 4 to about 80 amino acid residues. The inserts may represent, for example, a completely degenerate or biased array. Phage-bearing inserts that bind to the desired antigen are selected and this process repeated through several cycles of reselection
30 of phage that bind to the desired antigen. DNA sequencing is conducted to identify the sequences of the expressed peptides. The minimal linear portion of the sequence that binds to the desired antigen can be determined in this way. The procedure can be repeated using a biased library containing inserts containing part or all of the minimal linear portion plus one or more additional degenerate residues upstream or downstream thereof. These techniques may identify peptides of
35 the invention with still greater binding affinity for myostatin than agents already identified herein.

Regardless of the manner in which the peptides are prepared, a nucleic acid molecule encoding each such peptide can be generated using standard recombinant DNA procedures. The nucleotide sequence of such molecules can be manipulated as appropriate without changing the amino acid sequence they encode to account for the degeneracy of the nucleic acid code as well as to account for codon preference in particular host cells.

The present invention also provides nucleic acid molecules comprising polynucleotide sequences encoding the peptides and peptibodies of the present invention. These nucleic acid molecules include vectors and constructs containing polynucleotides encoding the peptides and peptibodies of the present invention, as well as peptide and peptibody variants and derivatives.

Exemplary nucleic acid molecules are provided in the Examples below.

Recombinant DNA techniques also provide a convenient method for preparing full length peptibodies and other large polypeptide binding agents of the present invention, or fragments thereof. A polynucleotide encoding the peptibody or fragment may be inserted into an expression vector, which can in turn be inserted into a host cell for production of the binding agents of the present invention. Preparation of exemplary peptibodies of the present invention are described in Example 2 below.

A variety of expression vector/host systems may be utilized to express the peptides and peptibodies of the invention. These systems include but are not limited to microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transfected with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmid); or animal cell systems. One preferred host cell line is *E.coli* strain 2596 (ATCC # 202174), used for expression of peptibodies as described below in Example 2. Mammalian cells that are useful in recombinant protein productions include but are not limited to VERO cells, HeLa cells, Chinese hamster ovary (CHO) cell lines, COS cells (such as COS-7), W138, BHK, HepG2, 3T3, RIN, MDCK, A549, PC12, K562 and 293 cells.

The term "expression vector" refers to a plasmid, phage, virus or vector, for expressing a polypeptide from a polynucleotide sequence. An expression vector can comprise a transcriptional unit comprising an assembly of (1) a genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers, (2) a structural or sequence that encodes the binding agent which is transcribed into mRNA and translated into protein, and (3) appropriate transcription initiation and termination sequences. Structural units intended for use in yeast or eukaryotic expression systems preferably include a leader sequence enabling extracellular

secretion of translated protein by a host cell. Alternatively, where recombinant protein is expressed without a leader or transport sequence, it may include an amino terminal methionyl residue. This residue may or may not be subsequently cleaved from the expressed recombinant protein to provide a final peptide product.

5 For example, the peptides and peptibodies may be recombinantly expressed in yeast using a commercially available expression system, *e.g.*, the Pichia Expression System (Invitrogen, San Diego, CA), following the manufacturer's instructions. This system also relies on the pre-pro-alpha sequence to direct secretion, but transcription of the insert is driven by the alcohol oxidase (AOX1) promoter upon induction by methanol. The secreted peptide is purified from the yeast
10 growth medium using the methods used to purify the peptide from bacterial and mammalian cell supernatants.

Alternatively, the cDNA encoding the peptide and peptibodies may be cloned into the baculovirus expression vector pVL1393 (PharMingen, San Diego, CA). This vector can be used according to the manufacturer's directions (PharMingen) to infect *Spodoptera frugiperda* cells in
15 sF9 protein-free media and to produce recombinant protein. The recombinant protein can be purified and concentrated from the media using a heparin-Sepharose column (Pharmacia).

Alternatively, the peptide or peptibody may be expressed in an insect system. Insect systems for protein expression are well known to those of skill in the art. In one such system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) can be used as a vector to express
20 foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The peptide coding sequence can be cloned into a nonessential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the peptide will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein coat. The recombinant viruses can be used to infect *S. frugiperda* cells or *Trichoplusia* larvae in which the
25 peptide is expressed (Smith *et al.*, *J Virol* 46: 584 (1983); Engelhard *et al.*, *Proc Nat Acad Sci (USA)* 91: 3224-7 (1994)).

In another example, the DNA sequence encoding the peptide can be amplified by PCR and cloned into an appropriate vector for example, pGEX-3X (Pharmacia). The pGEX vector is designed to produce a fusion protein comprising glutathione-S-transferase (GST), encoded by the
30 vector, and a protein encoded by a DNA fragment inserted into the vector's cloning site. The primers for PCR can be generated to include for example, an appropriate cleavage site. Where the fusion moiety is used solely to facilitate expression or is otherwise not desirable as an attachment to the peptide of interest, the recombinant fusion protein may then be cleaved from the GST portion of the fusion protein. The pGEX-3X/specific binding agent peptide construct is
35 transformed into *E. coli* XL-1 Blue cells (Stratagene, La Jolla CA), and individual transformants

isolated and grown. Plasmid DNA from individual transformants can be purified and partially sequenced using an automated sequencer to confirm the presence of the desired specific binding agent encoding nucleic acid insert in the proper orientation.

The fusion protein, which may be produced as an insoluble inclusion body in the bacteria,
5 can be purified as follows. Host cells are collected by centrifugation; washed in 0.15 M NaCl, 10 mM Tris, pH 8, 1 mM EDTA; and treated with 0.1 mg/ml lysozyme (Sigma, St. Louis, MO) for 15 minutes at room temperature. The lysate can be cleared by sonication, and cell debris can be pelleted by centrifugation for 10 minutes at 12,000 X g. The fusion protein-containing pellet can be resuspended in 50 mM Tris, pH 8, and 10 mM EDTA, layered over 50% glycerol, and
10 centrifuged for 30 min. at 6000 X g. The pellet can be resuspended in standard phosphate buffered saline solution (PBS) free of Mg⁺⁺ and Ca⁺⁺. The fusion protein can be further purified by fractionating the resuspended pellet in a denaturing SDS-PAGE (Sambrook *et al.*, *supra*). The gel can be soaked in 0.4 M KCl to visualize the protein, which can be excised and electroeluted in gel-running buffer lacking SDS. If the GST/fusion protein is produced in bacteria as a soluble
15 protein, it can be purified using the GST Purification Module (Pharmacia).

The fusion protein may be subjected to digestion to cleave the GST from the peptide of the invention. The digestion reaction (20-40 mg fusion protein, 20-30 units human thrombin (4000 U/mg, Sigma) in 0.5 ml PBS can be incubated 16-48 hrs at room temperature and loaded on a denaturing SDS-PAGE gel to fractionate the reaction products. The gel can be soaked in 0.4 M
20 KCl to visualize the protein bands. The identity of the protein band corresponding to the expected molecular weight of the peptide can be confirmed by amino acid sequence analysis using an automated sequencer (Applied Biosystems Model 473A, Foster City, CA). Alternatively, the identity can be confirmed by performing HPLC and/or mass spectrometry of the peptides.

Alternatively, a DNA sequence encoding the peptide can be cloned into a plasmid
25 containing a desired promoter and, optionally, a leader sequence (Better *et al.*, *Science* 240:1041-43 (1988)). The sequence of this construct can be confirmed by automated sequencing. The plasmid can then be transformed into *E. coli* strain MC1061 using standard procedures employing CaCl₂ incubation and heat shock treatment of the bacteria (Sambrook *et al.*, *supra*). The transformed bacteria can be grown in LB medium supplemented with carbenicillin, and
30 production of the expressed protein can be induced by growth in a suitable medium. If present, the leader sequence can effect secretion of the peptide and be cleaved during secretion.

Mammalian host systems for the expression of recombinant peptides and peptibodies are well known to those of skill in the art. Host cell strains can be chosen for a particular ability to process the expressed protein or produce certain post-translation modifications that will be useful
35 in providing protein activity. Such modifications of the protein include, but are not limited to,

acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation. Different host cells such as CHO, HeLa, MDCK, 293, WI38, and the like have specific cellular machinery and characteristic mechanisms for such post-translational activities and can be chosen to ensure the correct modification and processing of the introduced, foreign protein.

5 It is preferable that transformed cells be used for long-term, high-yield protein production. Once such cells are transformed with vectors that contain selectable markers as well as the desired expression cassette, the cells can be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The selectable marker is designed to allow growth and recovery of cells that successfully express the introduced sequences. Resistant
10 clumps of stably transformed cells can be proliferated using tissue culture techniques appropriate to the cell line employed.

A number of selection systems can be used to recover the cells that have been transformed for recombinant protein production. Such selection systems include, but are not limited to, HSV thymidine kinase, hypoxanthine-guanine phosphoribosyltransferase and adenine
15 phosphoribosyltransferase genes, in tk-, hgp^rt- or ap^rt- cells, respectively. Also, anti-metabolite resistance can be used as the basis of selection for dhfr which confers resistance to methotrexate; gpt which confers resistance to mycophenolic acid; neo which confers resistance to the aminoglycoside G418 and confers resistance to chlorsulfuron; and hyg^r which confers resistance to hygromycin. Additional selectable genes that may be useful include trpB, which allows cells to
20 utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine. Markers that give a visual indication for identification of transformants include anthocyanins, β -glucuronidase and its substrate, GUS, and luciferase and its substrate, luciferin.

Purification and Refolding of Binding Agents

25 In some cases, the binding agents such as the peptides and/or peptibodies of this invention may need to be "refolded" and oxidized into a proper tertiary structure and disulfide linkages generated in order to be biologically active. Refolding can be accomplished using a number of procedures well known in the art. Such methods include, for example, exposing the solubilized polypeptide agent to a pH usually above 7 in the presence of a chaotropic agent. The selection of
30 chaotrope is similar to the choices used for inclusion body solubilization, however a chaotrope is typically used at a lower concentration. Exemplary chaotropic agents are guanidine and urea. In most cases, the refolding/oxidation solution will also contain a reducing agent plus its oxidized form in a specific ratio to generate a particular redox potential which allows for disulfide shuffling to occur for the formation of cysteine bridges. Some commonly used redox couples include
35 cysteine/cystamine, glutathione/dithiobisGSH, cupric chloride, dithiothreitol DTT/dithiane DTT,

and 2-mercaptoethanol (bME)/dithio-bME. In many instances, a co-solvent may be used to increase the efficiency of the refolding. Commonly used cosolvents include glycerol, polyethylene glycol of various molecular weights, and arginine.

It may be desirable to purify the peptides and peptibodies of the present invention.

5 Protein purification techniques are well known to those of skill in the art. These techniques involve, at one level, the crude fractionation of the proteinaceous and non-proteinaceous fractions. Having separated the peptide and/or peptibody from other proteins, the peptide or polypeptide of interest can be further purified using chromatographic and electrophoretic techniques to achieve partial or complete purification (or purification to homogeneity). Analytical methods particularly
10 suited to the preparation of peptibodies and peptides or the present invention are ion-exchange chromatography, exclusion chromatography; polyacrylamide gel electrophoresis; isoelectric focusing. A particularly efficient method of purifying peptides is fast protein liquid chromatography or even HPLC.

Certain aspects of the present invention concern the purification, and in particular
15 embodiments, the substantial purification, of a peptibody or peptide of the present invention. The term "purified peptibody or peptide" as used herein, is intended to refer to a composition, isolatable from other components, wherein the peptibody or peptide is purified to any degree relative to its naturally-obtainable state. A purified peptide or peptibody therefore also refers to a peptibody or peptide that is free from the environment in which it may naturally occur.

20 Generally, "purified" will refer to a peptide or peptibody composition that has been subjected to fractionation to remove various other components, and which composition substantially retains its expressed biological activity. Where the term "substantially purified" is used, this designation will refer to a peptide or peptibody composition in which the peptibody or peptide forms the major component of the composition, such as constituting about 50%, about
25 60%, about 70%, about 80%, about 90%, about 95% or more of the proteins in the composition.

Various methods for quantifying the degree of purification of the peptide or peptibody will be known to those of skill in the art in light of the present disclosure. These include, for example, determining the specific binding activity of an active fraction, or assessing the amount of peptide or peptibody within a fraction by SDS/PAGE analysis. A preferred method for
30 assessing the purity of a peptide or peptibody fraction is to calculate the binding activity of the fraction, to compare it to the binding activity of the initial extract, and to thus calculate the degree of purification, herein assessed by a "-fold purification number." The actual units used to represent the amount of binding activity will, of course, be dependent upon the particular assay technique chosen to follow the purification and whether or not the peptibody or peptide exhibits a
35 detectable binding activity.

Various techniques suitable for use in purification will be well known to those of skill in the art. These include, for example, precipitation with ammonium sulphate, PEG, antibodies (immunoprecipitation) and the like or by heat denaturation, followed by centrifugation; chromatography steps such as affinity chromatography (*e.g.*, Protein-A-Sepharose), ion exchange, gel filtration, reverse phase, hydroxylapatite and affinity chromatography; isoelectric focusing; gel electrophoresis; and combinations of such and other techniques. As is generally known in the art, it is believed that the order of conducting the various purification steps may be changed, or that certain steps may be omitted, and still result in a suitable method for the preparation of a substantially purified binding agent.

There is no general requirement that the binding agents of the present invention always be provided in their most purified state. Indeed, it is contemplated that less substantially purified binding agent products will have utility in certain embodiments. Partial purification may be accomplished by using fewer purification steps in combination, or by utilizing different forms of the same general purification scheme. For example, it is appreciated that a cation-exchange column chromatography performed utilizing an HPLC apparatus will generally result in a greater "fold" purification than the same technique utilizing a low-pressure chromatography system. Methods exhibiting a lower degree of relative purification may have advantages in total recovery of the peptide or peptibody, or in maintaining binding activity of the peptide or peptibody.

It is known that the migration of a peptide or polypeptide can vary, sometimes significantly, with different conditions of SDS/PAGE (Capaldi *et al.*, *Biochem Biophys Res Comm*, 76: 425 (1977)). It will therefore be appreciated that under differing electrophoresis conditions, the apparent molecular weights of purified or partially purified binding agent expression products may vary.

Activity of Myostatin Binding Agents

After the construction of the binding agents of the present invention, they are tested for their ability to bind myostatin and inhibit or block myostatin activity. Any number of assays or animal tests may be used to determine the ability of the agent to inhibit or block myostatin activity. Several assays used for characterizing the peptides and peptibodies of the present invention are described in the Examples below. One assay is the C2C12 pMARE-luc assay which makes use of a myostatin-responsive cell line (C2C12 myoblasts) transfected with a luciferase reporter vector containing myostatin/activin response elements (MARE). Exemplary peptibodies are assayed by pre-incubating a series of peptibody dilutions with myostatin, and then exposing the cells to the incubation mixture. The resulting luciferase activity is determined, and a titration curve is generated from the series of peptibody dilutions. The IC_{50} (the concentration of

peptibody to achieve 50% inhibition of myostatin activity as measured by luciferase activity) was then determined. A second assay described below is a BIAcore® assay to determine the kinetic parameters k_a (association rate constant), k_d (dissociation rate constant), and K_D (dissociation equilibrium constant) for the myostatin binding agents. Lower dissociation equilibrium constants (K_D , expressed in nM) indicated a greater affinity of the peptibody for myostatin. Additional assays include blocking assays, to determine whether a binding agent such as a peptibody is neutralizing (prevents binding of myostatin to its receptor), or non-neutralizing (does not prevent binding of myostatin to its receptor); selectivity assays, which determine if the binding agents of the present invention bind selectively to myostatin and not to other TGF β family members; and KinEx A™ assays or solution-based equilibrium assays, which also determine K_D and are considered to be more sensitive in some circumstances. These assays are described in Example 3.

Figure 1 shows the IC_{50} of a peptide compared with the IC_{50} of the peptibody form of the peptide. This demonstrates that the peptibody is significantly more effective at inhibiting myostatin activity than the peptide alone. In addition, affinity-matured peptibodies generally exhibit improved IC_{50} and K_D values compared with the parent peptides and peptibodies. The IC_{50} values for a number of exemplary affinity matured peptibodies are shown in Table VII, Example 7 below. Additionally, in some instances, making a 2x version of a peptibody, where two peptides are attached in tandem, increase the activity of the peptibody both *in vitro* and *in vivo*.

In vivo activities are demonstrated in the Examples below. The activities of the binding agents include anabolic activity increasing lean muscle mass in animal models, as well as decreasing the fat mass with respect to total body weight in treated animal models, and increasing muscular strength in animal models.

Uses of the Myostatin Binding Agents

The myostatin binding agents of the present invention bind to myostatin and block or inhibit myostatin signaling within targeted cells. The present invention provides methods and reagents for reducing the amount or activity of myostatin in an animal by administering an effective dosage of one or more myostatin binding agents to the animal. In one aspect, the present invention provides methods and reagents for treating myostatin-related disorders in an animal comprising administering an effective dosage of one or more binding agents to the animal. These myostatin-related disorders include but are not limited to various forms of muscle wasting, as well as metabolic disorders such as diabetes and related disorders, and bone degenerative diseases such as osteoporosis.

As shown in the Example 8 below, exemplary peptibodies of the present invention dramatically increases lean muscle mass in the CD1 nu/nu mouse model. This *in vivo* activity correlates to the *in vitro* binding and inhibitory activity described below for the same peptibodies.

5 Muscle wasting disorders include dystrophies such as Duchenne's muscular dystrophy, progressive muscular dystrophy, Becker's type muscular dystrophy, Dejerine-Landouzy muscular dystrophy, Erb's muscular dystrophy, and infantile neuroaxonal muscular dystrophy. For example, blocking myostatin through use of antibodies *in vivo* improved the dystrophic phenotype of the *mdx* mouse model of Duchenne muscular dystrophy (Bogdanovich et al, *Nature* **420**, 28 (2002)). The peptibodies of the present invention increase lean muscle mass as a percentage of
10 body weight and decreases fat mass as percentage of body weight when administered to an aged *mdx* mouse model.

Additional muscle wasting disorders arise from chronic disease such as amyotrophic lateral sclerosis, congestive obstructive pulmonary disease, cancer, AIDS, renal failure, and rheumatoid arthritis. For example, cachexia or muscle wasting and loss of body weight was
15 induced in athymic nude mice by a systemically administered myostatin (Zimmers et al., *supra*). In another example, serum and intramuscular concentrations of myostatin-immunoreactive protein was found to be increased in men exhibiting AIDS-related muscle wasting and was inversely related to fat-free mass (Gonzalez-Cadavid et al., *PNAS USA* **95**: 14938-14943 (1998)). Additional conditions resulting in muscle wasting may arise from inactivity due to disability such
20 as confinement in a wheelchair, prolonged bedrest due to stroke, illness, spinal chord injury, bone fracture or trauma, and muscular atrophy in a microgravity environment (space flight). For example, plasma myostatin immunoreactive protein was found to increase after prolonged bedrest (Zachwieja et al. *J Gravit Physiol.* **6**(2):11(1999)). It was also found that the muscles of rats exposed to a microgravity environment during a space shuttle flight expressed an increased
25 amount of myostatin compared with the muscles of rats which were not exposed (Lalani et al., *J.Endocrin* **167** (3):417-28 (2000)).

In addition, age-related increases in fat to muscle ratios, and age-related muscular atrophy appear to be related to myostatin. For example, the average serum myostatin-immunoreactive protein increased with age in groups of young (19-35 yr old), middle-aged (36-75 yr old), and
30 elderly (76-92 yr old) men and women, while the average muscle mass and fat-free mass declined with age in these groups (Yarasheski et al. *J Nutr Aging* **6**(5):343-8 (2002)). It has also been shown that myostatin gene knockout in mice increased myogenesis and decreased adipogenesis (Lin et al., *Biochem Biophys Res Commun* **291**(3):701-6 (2002), resulting in adults with increased muscle mass and decreased fat accumulation and leptin secretion. Exemplary peptibodies
35 improve the lean muscle mass to fat ratio in aged *mdx* mice as shown below.

In addition, myostatin has now been found to be expressed at low levels in heart muscle and expression is upregulated after cardiomyocytes after infarct (Sharma et al., *J Cell Physiol.* 180 (1):1-9 (1999)). Therefore, reducing myostatin levels in the heart muscle may improve recovery of heart muscle after infarct.

5 Myostatin also appears to influence metabolic disorders including type 2 diabetes, noninsulin-dependent diabetes mellitus, hyperglycemia, and obesity. For example, lack of myostatin has been shown to improve the obese and diabetic phenotypes of two mouse models (Yen et al. *supra*). It has been demonstrated in the Examples below that decreasing myostatin activity by administering the inhibitors of the present invention will decrease the fat to muscle
10 ratio in an animal, including aged animal models. Therefore, decreasing fat composition by administering the inhibitors of the present invention will improve diabetes, obesity, and hyperglycemic conditions in animals.

 In addition, increasing muscle mass by reducing myostatin levels may improve bone strength and reduce osteoporosis and other degenerative bone diseases. It has been found, for
15 example, that myostatin-deficient mice showed increased mineral content and density of the mouse humerus and increased mineral content of both trabecular and cortical bone at the regions where the muscles attach, as well as increased muscle mass (Hamrick et al. *Calcif Tissue Int* 71(1):63-8 (2002)).

 The present invention also provides methods and reagents for increasing muscle mass in
20 food animals by administering an effective dosage of the myostatin binding agent to the animal. Since the mature C-terminal myostatin polypeptide is identical in all species tested, myostatin binding agents would be expected to be effective for increasing muscle mass and reducing fat in any agriculturally important species including cattle, chicken, turkeys, and pigs.

 The binding agents of the present invention may be used alone or in combination with
25 other therapeutic agents to enhance their therapeutic effects or decrease potential side effects. The binding agents of the present invention possess one or more desirable but unexpected combination of properties to improve the therapeutic value of the agents. These properties include increased activity, increased solubility, reduced degradation, increased half-life, reduced toxicity, and reduced immunogenicity. Thus the binding agents of the present invention are useful for
30 extended treatment regimes. In addition, the properties of hydrophilicity and hydrophobicity of the compounds of the invention are well balanced, thereby enhancing their utility for both *in vitro* and especially *in vivo* uses. Specifically, compounds of the invention have an appropriate degree of solubility in aqueous media that permits absorption and bioavailability in the body, while also having a degree of solubility in lipids that permits the compounds to traverse the cell membrane to
35 a putative site of action, such as a particular muscle mass.

The binding agents of the present invention are useful for treating a "subject" or any animal, including humans, when administered in an effective dosages in a suitable composition.

In addition, the myostatin binding agents of the present invention are useful for detecting and quantitating myostatin in a number of assays. These assays are described in more detail
5 below.

In general, the binding agents of the present invention are useful as capture agents to bind and immobilize myostatin in a variety of assays, similar to those described, for example, in Asai, ed., *Methods in Cell Biology*, 37, Antibodies in Cell Biology, Academic Press, Inc., New York (1993). The binding agent may be labeled in some manner or may react with a third molecule
10 such as an anti-binding agent antibody which is labeled to enable myostatin to be detected and quantitated. For example, a binding agent or a third molecule can be modified with a detectable moiety, such as biotin, which can then be bound by a fourth molecule, such as enzyme-labeled streptavidin, or other proteins. (Akerstrom, *J Immunol* 135:2589 (1985); Chaubert, *Mod Pathol* 10:585 (1997)).

15 Throughout any particular assay, incubation and/or washing steps may be required after each combination of reagents. Incubation steps can vary from about 5 seconds to several hours, preferably from about 5 minutes to about 24 hours. However, the incubation time will depend upon the assay format, volume of solution, concentrations, and the like. Usually, the assays will be carried out at ambient temperature, although they can be conducted over a range of
20 temperatures.

Non-competitive binding assays:

Binding assays can be of the non-competitive type in which the amount of captured myostatin is directly measured. For example, in one preferred "sandwich" assay, the binding agent can be bound directly to a solid substrate where it is immobilized. These immobilized
25 agents then bind to myostatin present in the test sample. The immobilized myostatin is then bound with a labeling agent, such as a labeled antibody against myostatin, which can be detected. In another preferred "sandwich" assay, a second agent specific for the binding agent can be added which contains a detectable moiety, such as biotin, to which a third labeled molecule can specifically bind, such as streptavidin. (See, Harlow and Lane, *Antibodies, A Laboratory Manual*,
30 Ch 14, Cold Spring Harbor Laboratory, NY (1988), which is incorporated herein by reference).

Competitive Binding Assays:

Binding assays can be of the competitive type. The amount of myostatin present in the sample is measured indirectly by measuring the amount of myostatin displaced, or competed away, from a binding agent by the myostatin present in the sample. In one preferred competitive

binding assay, a known amount of myostatin, usually labeled, is added to the sample and the sample is then contacted with the binding agent. The amount of labeled myostatin bound to the binding agent is inversely proportional to the concentration of myostatin present in the sample. (following the protocols found in, for example Harlow and Lane, Antibodies, A Laboratory

5 Manual, Ch 14, pp. 579-583, *supra*).

In another preferred competitive binding assay, the binding agent is immobilized on a solid substrate. The amount of myostatin bound to the binding agent may be determined either by measuring the amount of myostatin present in a myostatin/binding agent complex, or alternatively by measuring the amount of remaining uncomplexed myostatin.

10 Other Binding Assays

The present invention also provides Western blot methods to detect or quantify the presence of myostatin in a sample. The technique generally comprises separating sample proteins by gel electrophoresis on the basis of molecular weight and transferring the proteins to a suitable solid support, such as nitrocellulose filter, a nylon filter, or derivatized nylon filter. The sample is
15 incubated with the binding agents or fragments thereof that bind myostatin and the resulting complex is detected. These binding agents may be directly labeled or alternatively may be subsequently detected using labeled antibodies that specifically bind to the binding agent.

Diagnostic Assays

20 The binding agents or fragments thereof of the present invention may be useful for the diagnosis of conditions or diseases characterized by increased amounts of myostatin. Diagnostic assays for high levels of myostatin include methods utilizing a binding agent and a label to detect myostatin in human body fluids, extracts of cells or specific tissue extracts. For example, serum levels of myostatin may be measured in an individual over time to determine the onset of muscle
25 wasting associated with aging or inactivity, as described, for example, in Yarasheski et al., *supra*. Increased myostatin levels were shown to correlate with average decreased muscle mass and fat-free mass in groups of men and women of increasing ages (Yarasheski et al., *supra*). The binding agents of the present invention may be useful for monitoring increases or decreases in the levels of myostatin with a given individual over time, for example. The binding agents can be used in
30 such assays with or without modification. In a preferred diagnostic assay, the binding agents will be labeled by attaching, e.g., a label or a reporter molecule. A wide variety of labels and reporter molecules are known, some of which have been already described herein. In particular, the present invention is useful for diagnosis of human disease.

A variety of protocols for measuring myostatin proteins using binding agents of myostatin are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and fluorescence activated cell sorting (FACS).

For diagnostic applications, in certain embodiments the binding agents of the present invention typically will be labeled with a detectable moiety. The detectable moiety can be any one that is capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I , a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin; or an enzyme, such as alkaline phosphatase, β galactosidase, or horseradish peroxidase (Bayer et al., *Meth Enz*, **184**: 138 (1990)).

Pharmaceutical Compositions

Pharmaceutical compositions of myostatin binding agents such as peptibodies described herein are within the scope of the present invention. Such compositions comprise a therapeutically or prophylactically effective amount of a myostatin binding agent, fragment, variant, or derivative thereof as described herein, in admixture with a pharmaceutically acceptable agent. In a preferred embodiment, pharmaceutical compositions comprise antagonist binding agents that inhibit myostatin partially or completely in admixture with a pharmaceutically acceptable agent. Typically, the myostatin binding agents will be sufficiently purified for administration to an animal.

The pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. Suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates, other organic acids); bulking agents (such as mannitol or glycine), chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides and other carbohydrates (such as glucose, mannose, or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); coloring; flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such

as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (sucrose or sorbitol); tonicity enhancing agents
5 (such as alkali metal halides (preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. (Remington's Pharmaceutical Sciences, 18th Edition, A.R. Gennaro, ed., Mack Publishing Company, 1990).

The optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format, and desired
10 dosage. See for example, Remington's Pharmaceutical Sciences, supra. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the binding agent.

The primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection,
15 physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Other exemplary pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which may further include sorbitol or a suitable substitute therefore. In one embodiment of the
20 present invention, binding agent compositions may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (Remington's Pharmaceutical Sciences, supra) in the form of a lyophilized cake or an aqueous solution. Further, the binding agent product may be formulated as a lyophilizate using appropriate excipients such as sucrose.

25 The pharmaceutical compositions can be selected for parenteral delivery. Alternatively, the compositions may be selected for inhalation or for enteral delivery such as orally, aurally, ophthalmically, rectally, or vaginally. The preparation of such pharmaceutically acceptable compositions is within the skill of the art.

The formulation components are present in concentrations that are acceptable to the site
30 of administration. For example, buffers are used to maintain the composition at physiological pH or at slightly lower pH, typically within a pH range of from about 5 to about 8.

When parenteral administration is contemplated, the therapeutic compositions for use in this invention may be in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired binding agent in a pharmaceutically acceptable vehicle. A particularly
35 suitable vehicle for parenteral injection is sterile distilled water in which a binding agent is

formulated as a sterile, isotonic solution, properly preserved. Yet another preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (polylactic acid, polyglycolic acid), beads, or liposomes, that provides for the controlled or sustained release of the product which may then be delivered
5 via a depot injection. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Other suitable means for the introduction of the desired molecule include implantable drug delivery devices.

In another aspect, pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as
10 Hanks' solution, ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate,
15 triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. In another embodiment, a pharmaceutical composition may be formulated for inhalation. For example, a binding agent may be formulated as a dry powder for inhalation. Polypeptide or
20 nucleic acid molecule inhalation solutions may also be formulated with a propellant for aerosol delivery. In yet another embodiment, solutions may be nebulized. Pulmonary administration is further described in PCT Application No. PCT/US94/001875, which describes pulmonary delivery of chemically modified proteins.

It is also contemplated that certain formulations may be administered orally. In one
25 embodiment of the present invention, binding agent molecules that are administered in this fashion can be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. For example, a capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can
30 be included to facilitate absorption of the binding agent molecule. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders may also be employed.

Pharmaceutical compositions for oral administration can also be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral

administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active
5 compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums,
10 including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel,
15 polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations that can be used orally also include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or
20 sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Another pharmaceutical composition may involve an effective quantity of binding agent
25 in a mixture with non-toxic excipients that are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or other appropriate vehicle, solutions can be prepared in unit dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or
30 talc.

Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving binding agent molecules in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot
35 injections, are also known to those skilled in the art. See for example, PCT/US93/00829 that

describes controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions. Additional examples of sustained-release preparations include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides (U.S. 3,773,919, EP 58,481),
5 copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., *Biopolymers*, 22:547-556 (1983), poly (2-hydroxyethyl-methacrylate) (Langer et al., *J. Biomed. Mater. Res.*, 15:167-277, (1981); Langer et al., *Chem. Tech.*, 12:98-105(1982)), ethylene vinyl acetate (Langer et al., *supra*) or poly-D(-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomes, which can be prepared by any of several methods known in the art. See
10 e.g., Eppstein et al., *PNAS* (USA), 82:3688 (1985); EP 36,676; EP 88,046; EP 143,949.

The pharmaceutical composition to be used for *in vivo* administration typically must be sterile. This may be accomplished by filtration through sterile filtration membranes. Where the composition is lyophilized, sterilization using this method may be conducted either prior to or following lyophilization and reconstitution. The composition for parenteral administration may
15 be stored in lyophilized form or in solution. In addition, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or a dehydrated or lyophilized powder. Such
20 formulations may be stored either in a ready-to-use form or in a form (e.g., lyophilized) requiring reconstitution prior to administration.

In a specific embodiment, the present invention is directed to kits for producing a single-dose administration unit. The kits may each contain both a first container having a dried protein and a second container having an aqueous formulation. Also included within the scope of this
25 invention are kits containing single and multi-chambered pre-filled syringes (e.g., liquid syringes and lyosyringes).

An effective amount of a pharmaceutical composition to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will thus vary depending, in part, upon
30 the molecule delivered, the indication for which the binding agent molecule is being used, the route of administration, and the size (body weight, body surface or organ size) and condition (the age and general health) of the patient. Accordingly, the clinician may titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage may range from about 0.1mg/kg to up to about 100 mg/kg or more, depending on the factors mentioned

above. In other embodiments, the dosage may range from 0.1 mg/kg up to about 100 mg/kg; or 1 mg/kg up to about 100 mg/kg; or 5 mg/kg up to about 100 mg/kg.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays or in animal models such as mice, rats, rabbits, dogs, pigs, or monkeys. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

The exact dosage will be determined in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active compound or to maintain the desired effect. Factors that may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

The frequency of dosing will depend upon the pharmacokinetic parameters of the binding agent molecule in the formulation used. Typically, a composition is administered until a dosage is reached that achieves the desired effect. The composition may therefore be administered as a single dose, or as multiple doses (at the same or different concentrations/dosages) over time, or as a continuous infusion. Further refinement of the appropriate dosage is routinely made. Appropriate dosages may be ascertained through use of appropriate dose-response data.

The route of administration of the pharmaceutical composition is in accord with known methods, e.g. orally, through injection by intravenous, intraperitoneal, intracerebral (intraparenchymal), intracerebroventricular, intramuscular, intra-ocular, intraarterial, intraportal, intralesional routes, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, urethral, vaginal, or rectal means, by sustained release systems or by implantation devices. Where desired, the compositions may be administered by bolus injection or continuously by infusion, or by implantation device.

Alternatively or additionally, the composition may be administered locally via implantation of a membrane, sponge, or another appropriate material on to which the desired molecule has been absorbed or encapsulated. Where an implantation device is used, the device may be implanted into any suitable tissue or organ, and delivery of the desired molecule may be via diffusion, timed-release bolus, or continuous administration.

In some cases, it may be desirable to use pharmaceutical compositions in an *ex vivo* manner. In such instances, cells, tissues, or organs that have been removed from the patient are exposed to the pharmaceutical compositions after which the cells, tissues and/or organs are subsequently implanted back into the patient.

5 In other cases, a binding agent of the present invention such as a peptibody can be delivered by implanting certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the polypeptide. Such cells may be animal or human cells, and may be autologous, heterologous, or xenogeneic. Optionally, the cells may be immortalized. In order to decrease the chance of an immunological response, the cells may be
10 encapsulated to avoid infiltration of surrounding tissues. The encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the protein product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

Pharmaceutical compositions containing the binding agents of the present invention are
15 administered to a subject to treat any myostatin-related disorders. These include muscle-wasting disorders including but not limited to muscular dystrophy, muscle wasting in cancer, AIDS, muscle atrophy, rheumatoid arthritis, renal failure/uremia, chronic heart failure, prolonged bed-rest, spinal chord injury, stroke, and aging related sarcopenia. In addition these compositions are administered to treat obesity, diabetes, hyperglycemia, and increase bone density,
20

The invention having been described, the following examples are offered by way of illustration, and not limitation.

Example 1

25 Identification of myostatin -binding peptides

Three filamentous phage libraries, TN8-IX (5×10^9 independent transformants), TN12-I (1.4×10^9 independent transformants), and linear (2.3×10^9 independent transformants) (Dyax Corp.) were used to select for myostatin binding phage. Each library was incubated on myostatin-coated surfaces and subjected to different panning conditions: non-specific elution, and specific
30 elution using recombinant human activin receptor IIB/Fc chimera (R&D Systems, Inc., Minneapolis, Minnesota), or myostatin propeptide elution as described below. For all three libraries, the phages were eluted in a non-specific manner for the first round of selection, while the receptor and promyostatin was used in the second and third rounds of selection. The selection procedures were carried out as described below.

Preparation of myostatin

Myostatin protein was produced recombinantly in the *E. coli* K-12 strain 2596 (ATCC # 202174) as follows. Polynucleotides encoding the human promyostatin molecule were cloned
5 into the pAMG21 expression vector (ATCC No. 98113), which was derived from expression
vector pCFM1656 (ATCC No. 69576) and the expression vector system described in United
States Patent No. 4,710,473, by following the procedure described in published International
Patent Application WO 00/24782. The polynucleotides encoding promyostatin were obtained
10 from a mammalian expression vector. The coding region was amplified using a standard PCR
method and the following PCR primers to introduce the restriction site for *NdeI* and *BamHI*.
5' primer: 5'-GAGAGAGAGCATATGAATGAGAACAGTGAGCAAAAAG-3' (Seq ID No:
292)

3' primer: 5'-AGAGAGGGATCCATTATGAGCACCCACAGCGGTC-3' (Seq ID No: 293)

The PCR product and vector were digested with both enzymes, mixed and ligated. The
15 product of the ligation was transformed into *E. coli* strain #2596. Single colonies were checked
microscopically for recombinant protein expression in the form of inclusion bodies. The plasmid
was isolated and sequenced through the coding region of the recombinant gene to verify genetic
fidelity.

Bacterial paste was generated from a 10L fermentation using a batch method at 37°C.
20 The culture was induced with HSL at a cell density of 9.6 OD₆₀₀ and harvested six hours later at a
density of 104 OD₆₀₀. The paste was stored at -80°C. *E. coli* paste expressing promyostatin was
lysed in a microfluidizer at 16,000psi, centrifuged to isolate the insoluble inclusion body fraction.
Inclusion bodies were resuspended in guanidine hydrochloride containing dithiothreitol and
solubilized at room temperature. This was then diluted 30 fold in an aqueous buffer. The
25 refolded promyostatin was then concentrated and buffer exchanged into 20mM Tris pH 8.0, and
applied to an anion exchange column. The anion exchange column was eluted with an increasing
sodium chloride gradient. The fractions containing promyostatin were pooled. The promyostatin
produced in *E. coli* is missing the first 23 amino acids and begins with a methionine before the
residue 24 asparagine. To produce mature myostatin, the pooled promyostatin was enzymatically
30 cleaved between the propeptide and mature myostatin C terminal. The resulting mixture was then
applied to a C4-rpHPLC column using a increasing gradient of acetonitrile containing 0.1%
trifluoroacetic acid. Fractions containing mature myostatin were pooled and dried in a speed-vac.

The recombinant mature myostatin produced from *E. coli* was tested in the myoblast
C2C12 based assay described below and found to be fully active when compared with

recombinant murine myostatin commercially produced in a mammalian cell system (R&D Systems, Inc., Minneapolis, Minnesota). The *E.coli*-produced mature myostatin was used in the phage-display and screening assays described below.

Preparation of Myostatin-Coated Tubes

5 Myostatin was immobilized on 5 ml Immuno™ Tubes (NUNC) at a concentration of 8 ug of myostatin protein in 1 ml of 0.1M sodium carbonate buffer (pH 9.6). The myostatin-coated Immuno™ Tube was incubated with orbital shaking for 1 hour at room temperature. Myostatin-coated Immuno™ Tube was then blocked by adding 5 ml of 2% milk-PBS and incubating at room temperature for 1 hour with rotation. The resulting myostatin-coated Immuno™ Tube was
10 then washed three times with PBS before being subjected to the selection procedures. Additional Immuno™ Tubes were also prepared for negative selections (no myostatin). For each panning condition, five to ten Immuno™ Tubes were subjected to the above procedure except that the Immuno™ Tubes were coated with 1ml of 2% BSA-PBS instead of myostatin protein.

Negative Selection

15 For each panning condition, about 100 random library equivalents for TN8-IX and TN12-I libraries (5×10^{11} pfu for TN8-IX, and 1.4×10^{11} pfu for TN12-I) and about 10 random library equivalents for the linear library (2.3×10^{10} pfu) were aliquoted from the library stock and diluted to 1 ml with PBST (PBS with 0.05% Tween-20). The 1 ml of diluted library stock was added to an Immuno™ Tube prepared for the negative selection, and incubated for 10 minutes at room
20 temperature with orbital shaking. The phage supernatant was drawn out and added to the second Immuno™ Tube for another negative selection step. In this way, five to ten negative selection steps were performed.

Selection for Myostatin Binding

25 After the last negative selection step above, the phage supernatant was added to the prepared myostatin coated Immuno™ Tubes. The Immuno™ Tube was incubated with orbital shaking for one hour at room temperature, allowing specific phage to bind to myostatin. After the supernatant was discarded, the Immuno™ Tube was washed about 15 times with 2% milk-PBS, 10 times with PBST and twice with PBS for the three rounds of selection with all three libraries (TN8-IX, TN12-I, and Linear libraries) except that for the second round of selections with TN8-
30 IX and TN12-I libraries, the Immuno™ Tube was washed about 14 times with 2% milk-PBS, twice with 2% BSA-PBS, 10 times with PBST and once with PBS.

Non-specific elution

After the last washing step, the bound phages were eluted from the Immuno™ Tube by adding 1 ml of 100 mM triethylamine solution (Sigma, St. Louis, Missouri) with 10-minute

incubation with orbital shaking. The pH of the phage containing solution was then neutralized with 0.5 ml of 1 M Tris-HCl (pH 7.5).

Receptor (Human Activin Receptor) elution of bound phage

- For round 2 and 3, after the last washing step, the bound phages were eluted from the
- 5 Immuno™ Tube by adding 1 ml of 1 μ M of receptor protein (recombinant human activin receptor IIB/Fc chimera, R&D Systems, Inc., Minneapolis, Minnesota) with a 1-hour incubation for each condition.

Propeptide elution of bound phage

- For round 2 and 3, after the last washing step, the bound phages were eluted from the
- 10 Immuno™ Tube by adding 1 ml of 1 μ M propeptide protein (made as described above) with a 1-hour incubation for each condition.

Phage Amplification

- Fresh *E.coli*. (XL-1 Blue MRF") culture was grown to $OD_{600} = 0.5$ in LB media containing 12.5 μ g/ml tetracycline. For each panning condition, 20 ml of this culture was chilled
- 15 on ice and centrifuged. The bacteria pellet was resuspended in 1 ml of the min A salts solution.

- Each mixture from different elution methods was added to a concentrated bacteria sample and incubated at 37°C for 15 minutes. 2 ml of NZCYM media (2x NZCYM, 50 μ g/ml Ampicillin) was added to each mixture and incubated at 37°C for 15 minutes. The resulting 4 ml solution was plated on a large NZCYM agar plate containing 50 μ g/ml ampicillin and incubated
- 20 overnight at 37°C.

- Each of the bacteria/phage mixture that was grown overnight on a large NZCYM agar plate was scraped off in 35 ml of LB media, and the agar plate was further rinsed with additional 35 ml of LB media. The resulting bacteria/phage mixture in LB media was centrifuged to pellet the bacteria away. 50 μ l of the phage supernatant was transferred to a fresh tube, and 12.5 ml of
- 25 PEG solution (20% PEG8000, 3.5M ammonium acetate) was added and incubated on ice for 2 hours to precipitate phages. The precipitated phages were centrifuged down and resuspended in 6 ml of the phage resuspension buffer (250 mM NaCl, 100 mM Tris pH8, 1 mM EDTA). This phage solution was further purified by centrifuging away the remaining bacteria and precipitating the phage for the second time by adding 1.5 ml of the PEG solution. After a centrifugation step,
- 30 the phage pellet was resuspended in 400 μ l of PBS. This solution was subjected to a final centrifugation to rid of remaining bacteria debris. The resulting phage preparation was titered by a standard plaque formation assay (Molecular Cloning, Maniatis et al., 3rd Edition).

Additional rounds of selection and amplification

In the second round, the amplified phage (10^{11} pfu) from the first round was used as the input phage to perform the selection and amplification steps. The amplified phage (10^{11} pfu) from the second round in turn was used as the input phage to perform third round of selection and amplification. After the elution steps of the third round, a small fraction of the eluted phage was
5 plated out as in the plaque formation assay above. Individual plaques were picked and placed into 96 well microtiter plates containing 100 μ l of TE buffer in each well. These master plates were incubated at 4°C overnight to allow phages to elute into the TE buffer.

Clonal Analysis

Phage ELISA

10 The phage clones were subjected to phage ELISA and then sequenced. The sequences were ranked as discussed below.

Phage ELISA was performed as follows. An *E. Coli* XL-1 Blue MRF' culture was grown until OD₆₀₀ reached 0.5. 30 μ l of this culture was aliquoted into each well of a 96 well microtiter plate. 10 μ l of eluted phage was added to each well and allowed to infect bacteria for 15 min at
15 room temperature. About 120 μ l of LB media containing 12.5 μ g/ml of tetracycline and 50 μ g/ml of ampicillin were added to each well. The microtiter plate was then incubated with shaking overnight at 37 °C. Myostatin protein (2 μ g/ml in 0.1M sodium carbonate buffer, pH 9.6) was allowed to coat onto a 96 well Maxisorp™ plates (NUNC) overnight at 4°C. As a control, a separate Maxisorp™ plate was coated with 2% BSA prepared in PBS.

20 On the following day, liquid in the protein coated Maxisorp™ plates was discarded, washed three times with PBS and each well was blocked with 300 μ l of 2% milk solution at room temperature for 1 hour. The milk solution was discarded, and the wells were washed three times with the PBS solution. After the last washing step, about 50 μ l of PBST-4% milk was added to each well of the protein-coated Maxisorp™ plates. About 50 μ l of overnight cultures from each
25 well in the 96 well microtiter plate was transferred to the corresponding wells of the myostatin coated plates as well as the control 2% BSA coated plates. The 100 μ l mixture in the two kinds of plates were incubated for 1 hour at room temperature. The liquid was discarded from the Maxisorp™ plates, and the wells were washed about three times with PBST followed by two times with PBS. The HRP-conjugated anti-M13 antibody (Amersham Pharmacia Biotech) was
30 diluted to about 1:7,500, and 100 μ l of the diluted solution was added to each well of the Maxisorp™ plates for 1 hour incubation at room temperature. The liquid was again discarded and the wells were washed about three times with PBST followed by two time with PBS. 100 μ l of LumiGlo™ Chemiluminescent substrate (KPL) was added to each well of the Maxisorp™ plates and incubated for about 5 minutes for reaction to occur. The chemiluminescent unit of the
35 Maxisorp™ plates was read on a plate reader (Lab System).

Sequencing of the phage clones

For each phage clone, the sequencing template was prepared by a PCR method. The following oligonucleotide pair was used to amplify a 500 nucleotide fragment: primer #1: 5'-CGGCGCAACTATCGGTATCAAGCTG-3' (Seq ID No: 294) and primer #2: 5'-CATGTACCGTAACACTGAGTTTCGTC-3' (Seq ID No: 295). The following mixture was prepared for each clone.

| Reagents | Volume (μL) / tube |
|---|--------------------|
| distilled H ₂ O | 26.25 |
| 50% glycerol | 10 |
| 10X PCR Buffer (w/o MgCl ₂) | 5 |
| 25 mM MgCl ₂ | 4 |
| 10 mM dNTP mix | 1 |
| 100 μM primer 1 | 0.25 |
| 100 μM primer 2 | 0.25 |
| Taq polymerase | 0.25 |
| Phage in TE (section 4) | 3 |
| Final reaction volume | 50 |

A thermocycler (GeneAmp PCR System 9700, Applied Biosystem) was used to run the following program: [94°C for 5min; 94°C for 30 sec, 55°C for 30 sec, 72°C for 45 sec.] x30 cycles; 72°C for 7 min; cool to 4°C. The PCR product from each reaction was cleaned up using the QIAquick Multiwell PCR Purification kit (Qiagen), following the manufacturer's protocol. The PCR cleaned up product was checked by running 10 ul of each PCR reaction mixed with 1 ul of dye (10X BBXS agarose gel loading dye) on a 1% agarose gel. The remaining product was then sequenced using the ABI 377 Sequencer (Perkin Elmer) following the manufacturer recommended protocol.

Sequence Ranking and Analysis

The peptide sequences that were translated from the nucleotide sequences were correlated to ELISA data. The clones that showed high chemiluminescent units in the myostatin-coated wells and low chemiluminescent units in the 2% BSA-coated wells were identified. The sequences that occurred multiple times were identified. Candidate sequences chosen based on these criteria were subjected to further analysis as peptibodies. Approximately 1200 individual clones were analyzed. Of these approximately 132 peptides were chosen for generating the peptibodies of the present invention. These are shown in Table I below. The peptides having

SEQ ID NO: 1 to 129 were used to generate peptibodies of the same name. The peptides having SEQ ID NO: 130 to 141 shown in Table 1 comprise two or more peptides from SEQ ID NO: 1 to 132 attached by a linker sequence. SEQ ID NO: 130 to 141 were also used to generate peptibodies of the same name.

- 5 Consensus sequences were determined for the TN-8 derived group of peptides. These are as follows:

KDXCXXWHWMCKPX (Seq ID No: 142)

WXXCXXXGFWCXNX (Seq ID No: 143)

IXGCXWWDXXCYXX (Seq ID No: 144)

10 XXWCVSPXWFCXXX (Seq ID No: 145)

XXXCPWFAXXCVDW (Seq ID No: 146)

- For all of the above consensus sequences, the underlined "core sequences" from each consensus sequence are the amino acid which always occur at that position. "X" refers to any naturally occurring or modified amino acid. The two cysteines contained with the core sequences were
15 fixed amino acids in the TN8-IX library.

TABLE I

PEPTIBODY NAME SEQ.ID No PEPTIDE SEQUENCE

| | | |
|---------------------|----|-----------------|
| Myostatin-TN8-Con1 | 1 | KDKCKMWHWMCKPP |
| Myostatin-TN8-Con2 | 2 | KDLCAMWHWMCKPP |
| Myostatin-TN8-Con3 | 3 | KDLCKMWKWMCKPP |
| Myostatin-TN8-Con4 | 4 | KDLCKMWHWMCKPK |
| Myostatin-TN8-Con5 | 5 | WYPCYEFHFWCYDL |
| Myostatin-TN8-Con6 | 6 | WYPCYEGHFWCYDL |
| Myostatin-TN8-Con7 | 7 | IFGCKWWDVQCYQF |
| Myostatin-TN8-Con8 | 8 | IFGCKWWDVDCYQF |
| Myostatin-TN8-Con9 | 9 | ADWCVSPNWFCMVM |
| Myostatin-TN8-Con10 | 10 | HKFCPWWALFCWDF |
| Myostatin-TN8-1 | 11 | KDLCKMWHWMCKPP |
| Myostatin-TN8-2 | 12 | IDKCAIWGWMCPPPL |
| Myostatin-TN8-3 | 13 | WYPCGEFGMWCLNV |
| Myostatin-TN8-4 | 14 | WFTCLWNCNE |
| Myostatin-TN8-5 | 15 | HTPCPWFAPLCVEW |
| Myostatin-TN8-6 | 16 | KEWCWRWKWMCKPE |
| Myostatin-TN8-7 | 17 | FETCPSWAYFCLDI |
| Myostatin-TN8-8 | 18 | AYKCEANDWGCWWL |
| Myostatin-TN8-9 | 19 | NSWCEDQWHRCWWL |
| Myostatin-TN8-10 | 20 | WSACYAGHFWCYDL |
| Myostatin-TN8-11 | 21 | ANWCVSPNWFCMVM |
| Myostatin-TN8-12 | 22 | WTECYQQEFWCWNL |
| Myostatin-TN8-13 | 23 | ENTCERWKWMCPPK |
| Myostatin-TN8-14 | 24 | WLPCHQEGFWCMNF |
| Myostatin-TN8-15 | 25 | STMCSQWHWMCNPF |

| | | |
|-------------------|----|---------------------|
| Myostatin-TN8-16 | 26 | IFGCHWWDVDCYQF |
| Myostatin-TN8-17 | 27 | IYGCKWWDIQCYDI |
| Myostatin-TN8-18 | 28 | PDWCIDPDWWCKFW |
| Myostatin-TN8-19 | 29 | QGHCTRWPWMCPPY |
| Myostatin-TN8-20 | 30 | WQECYREGFWCLQT |
| Myostatin-TN8-21 | 31 | WFDCYGPFGKWCSP |
| Myostatin-TN8-22 | 32 | GVRCPKGHLWCLYP |
| Myostatin-TN8-23 | 33 | HWACGYWPWSCWV |
| Myostatin-TN8-24 | 34 | GPACHSPWWCVFG |
| Myostatin-TN8-25 | 35 | TTWCISPMWFCSQQ |
| Myostatin-TN8-26 | 36 | HKFCPPWAIFCWDF |
| Myostatin-TN8-27 | 37 | PDWCVSPRWYCNMW |
| Myostatin-TN8-28 | 38 | VWKCHWFGMDCEPT |
| Myostatin-TN8-29 | 39 | KKHCQIWTWMCAPK |
| Myostatin-TN8-30 | 40 | WFQCGSTLFWCYNL |
| Myostatin-TN8-31 | 41 | WSPCYDHYFYCYTI |
| Myostatin-TN8-32 | 42 | SWMCGFFKEVCMWV |
| Myostatin-TN8-33 | 43 | EMLCMIHPVFCNPH |
| Myostatin-TN8-34 | 44 | LKTCNLWPWMCPL |
| Myostatin-TN8-35 | 45 | VVGCKWYEAWCYNK |
| Myostatin-TN8-36 | 46 | PIHCTQWAWMCPPT |
| Myostatin-TN8-37 | 47 | DSNCPWYFLSCVIF |
| Myostatin-TN8-38 | 48 | HIWCNLAMMKCVEM |
| Myostatin-TN8-39 | 49 | NLQCIYFLGKCIYF |
| Myostatin-TN8-40 | 50 | AWRCMWFSDVCTPG |
| Myostatin-TN8-41 | 51 | WFRCLDADWCTSV |
| Myostatin-TN8-42 | 52 | EKICQMWSWMCAPP |
| Myostatin-TN8-43 | 53 | WFYCHLNKSECTEP |
| Myostatin-TN8-44 | 54 | FWRCAIGIDKCKRV |
| Myostatin-TN8-45 | 55 | NLGCKWYEVWCFTY |
| Myostatin-TN8-46 | 56 | IDLCNMWDGMCYPP |
| Myostatin-TN8-47 | 57 | EMPCNIWGWMCPPV |
| Myostatin-TN12-1 | 58 | WFRCVLTGIVDWSECFGL |
| Myostatin-TN12-2 | 59 | GFSCFTGLDEFYVDCSPF |
| Myostatin-TN12-3 | 60 | LPWCHDQVNADWGFCMLW |
| Myostatin-TN12-4 | 61 | YPTCSEKFWTYGQTCVLW |
| Myostatin-TN12-5 | 62 | LGPCPIHHGPWPQYCVYW |
| Myostatin-TN12-6 | 63 | PFPCEHQISWLGHCLSF |
| Myostatin-TN12-7 | 64 | HWGCEDLMWSWHPLCRRP |
| Myostatin-TN12-8 | 65 | LPLCDADMMPTIGFCVAY |
| Myostatin-TN12-9 | 66 | SHWCETTFWMNYAKCVHA |
| Myostatin-TN12-10 | 67 | LPKCTHVPFDQGGFCLWY |
| Myostatin-TN12-11 | 68 | FSSCWSPVSRQDMFCVYF |
| Myostatin-TN12-13 | 69 | SHKCEYSGWLQPLCYRP |
| Myostatin-TN12-14 | 70 | PWWCQDNYVQHMLHCDSP |
| Myostatin-TN12-15 | 71 | WFRCLMLNSFDAFCVSY |
| Myostatin-TN12-16 | 72 | PDACRDQPWYMFMGCM LG |
| Myostatin-TN12-17 | 73 | FLACFVEFELCFDS |
| Myostatin-TN12-18 | 74 | SAYCITESDPYVLCVPL |

| | | |
|---------------------|-----|----------------------|
| Myostatin-TN12-19 | 75 | PSICESYSTMWLPMCQHN |
| Myostatin-TN12-20 | 76 | WLDCHDDSWAWTKMCRSH |
| Myostatin-TN12-21 | 77 | YLNCVMMNTSPFVECVFN |
| Myostatin-TN12-22 | 78 | YPWCDGFMIQQGITCMFY |
| Myostatin-TN12-23 | 79 | FDYCTWLNGFKDWKCWSR |
| Myostatin-TN12-24 | 80 | LPLCNLKEISHVQACVLF |
| Myostatin-TN12-25 | 81 | SPECAFARWLGIEQCQRD |
| Myostatin-TN12-26 | 82 | YPQCFNLHLEWTECDWF |
| Myostatin-TN12-27 | 83 | RWRCEIYDSEFLPKCWFF |
| Myostatin-TN12-28 | 84 | LVGCDNVWHRCKLF |
| Myostatin-TN12-29 | 85 | AGWCHVWGEMFGMGCSAL |
| Myostatin-TN12-30 | 86 | HHECEWMARWMSLDCVGL |
| Myostatin-TN12-31 | 87 | FPMCGLAGMKDFDFCVWY |
| Myostatin-TN12-32 | 88 | RDDCTFWPEWLWKLCEP |
| Myostatin-TN12-33 | 89 | YNFCSYLFGVSKEACQLP |
| Myostatin-TN12-34 | 90 | AHWCEQGPWRYGNICMAY |
| Myostatin-TN12-35 | 91 | NLVCGKISAWGDEACARA |
| Myostatin-TN12-36 | 92 | HNVCITMGPSMKWFCWND |
| Myostatin-TN12-37 | 93 | NDLCAMWGWWRNTIWCQNS |
| Myostatin-TN12-38 | 94 | PPFCQNDNDMLQSLCKLL |
| Myostatin-TN12-39 | 95 | WYDCNVPNELLSGLCRLF |
| Myostatin-TN12-40 | 96 | YGDCDQNHWMWPFTCLSL |
| Myostatin-TN12-41 | 97 | GWMCHFDLHDWGATCQPD |
| Myostatin-TN12-42 | 98 | YFHCMTFGGHEFEVHCESF |
| Myostatin-TN12-43 | 99 | AYWCWHGQCVRF |
| Myostatin-Linear-1 | 100 | SEHWTFTDWDGNEWVVRPF |
| Myostatin-Linear-2 | 101 | MEMLDSLFECLKDMVPISKA |
| Myostatin-Linear-3 | 102 | SPPEEALMEWLGWQYGKFT |
| Myostatin-Linear-4 | 103 | SPENLLNDLYILMTKQEWYG |
| Myostatin-Linear-5 | 104 | FHWEEGIPFHVVTPTYSDRM |
| Myostatin-Linear-6 | 105 | KRLLEQFMNDLAEVSGHS |
| Myostatin-Linear-7 | 106 | DTRDALFOEFYEFVRSRLVI |
| Myostatin-Linear-8 | 107 | RMSAAPRPLTYRDIMDQYWH |
| Myostatin-Linear-9 | 108 | NDKAHFFEMFMFDVHNFVES |
| Myostatin-Linear-10 | 109 | QTQAQKIDGLWELLQSIRNQ |
| Myostatin-Linear-11 | 110 | MLSEFEEFLGNLVHRQEA |
| Myostatin-Linear-12 | 111 | YTPKMGSEWTSFWHNRIHYL |
| Myostatin-Linear-13 | 112 | LNDTLLRELKMVLNSLSDMK |
| Myostatin-Linear-14 | 113 | FDVERDLMRWLEGFMQSAAT |
| Myostatin-Linear-15 | 114 | HHGWNYLRKGSAPQWFPAWV |
| Myostatin-Linear-16 | 115 | VESLHQLQMWLDQKLASGPH |
| Myostatin-Linear-17 | 116 | RATLLKDFWQLVEGYGDN |
| Myostatin-Linear-18 | 117 | EELLREFYRFVSAFDY |
| Myostatin-Linear-19 | 118 | GLLDEFSHFIAEQFYQMPGG |
| Myostatin-Linear-20 | 119 | YREMSMLEGLLDVLERLQHY |
| Myostatin-Linear-21 | 120 | HNSSQMLLSELIMLVGSMQ |
| Myostatin-Linear-22 | 121 | WREHFLNSDYIRDKLIADG |
| Myostatin-Linear-23 | 122 | QFPFYVFDDLPAQLEYWIA |

| | | |
|-------------------------|-----|---|
| Myostatin-Linear-24 | 123 | EFFHWLHNHRSEVNHWLDMN |
| Myostatin-Linear-25 | 124 | EALFQNFVRDVLTLSEREY |
| Myostatin-Linear-26 | 125 | QYWEQQWMTYFRENGLHVQY |
| Myostatin-Linear-27 | 126 | NQRMMLLEDLWRIMTPMFGRS |
| Myostatin-Linear-29 | 127 | FLDELKAELSRHYALDDLDE |
| Myostatin-Linear-30 | 128 | GKLIEGLLNELMQLETMPD |
| Myostatin-Linear-31 | 129 | ILLLEYKDKWKSWF |
| Myostatin-2xTN8-19 kc | 130 | QGHCTRWPWMCPPYGSGSATGGS GSTASSGSGSATGQGHCTRWPWM CPPY |
| Myostatin-2xTN8-con6 | 131 | WYPCYEGHFWCYDLGSGSTASSG SGSATGWYPCYEGHFWCYDL |
| Myostatin-2xTN8-5 kc | 132 | HTPCPWFAPLCVEWGSGSATGGSG STASSGSGSATGHTPCPWFAPLCV EW |
| Myostatin-2xTN8-18 kc | 133 | PDWCIDPDWWCKFWGSGSATGGS GSTASSGSGSATGPDWCIDPDWW CKFW |
| Myostatin-2xTN8-11 kc | 134 | ANWCVSPNWF CMVMGSGSATGG SGSTASSGSGSATGANWCVSPNWF CMVM |
| Myostatin-2xTN8-25 kc | 135 | PDWCIDPDWWCKFWGSGSATGGS GSTASSGSGSATGPDWCIDPDWW CKFW |
| Myostatin-2xTN8-23 kc | 136 | HWACGYWPWSCKWVGSGSATGG SGSTASSGSGSATGHWACGYWPW SCKWV |
| Myostatin-TN8-29-19 kc | 137 | KKHCQIWTWMCAPKGSGSATGGS GSTASSGSGSATGQGHCTRWPWM CPPY |
| Myostatin-TN8-19-29 kc | 138 | QGHCTRWPWMCPPYGSGSATGGS GSTASSGSGSATGKKHCQIWTWM CAPK |
| Myostatin-TN8-29-19 kn | 139 | KKHCQIWTWMCAPKGSGSATGGS GSTASSGSGSATGQGHCTRWPWM CPPY |
| Myostatin-TN8-29-19-8g | 140 | KKHCQIWTWMCAPKGGGGGGGG QGHCTRWPWMCPPY |
| Myostatin-TN8-19-29-6gc | 141 | QGHCTRWPWMCPPYGGGGGGGKK HCQIWTWMCAPK |

Example 2

Generating peptibodies

5 Construction of DNA encoding peptide-Fc fusion proteins

Peptides capable of binding myostatin were used alone or in combination with each other to construct fusion proteins in which a peptide was fused to the Fc domain of human IgG1. The

amino acid sequence of the Fc portion of each peptibody is as follows (from amino terminus to carboxyl terminus):

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
 SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
 5 HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
 RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVL
 DSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLS
 LSPGK (Seq ID No: 296)

The peptide was fused in the N configuration (peptide was attached to the N-terminus of the Fc region), the C configuration (peptide was attached to the C-terminus of the Fc region), or the N,C configuration (peptide attached both at the N and C terminus of the Fc region). Separate vectors were used to express N-terminal fusions and C-terminal fusions. Each peptibody was constructed by annealing pairs of oligonucleotides ("oligos") to the selected phage nucleic acid to generate a double stranded nucleotide sequence encoding the peptide. These polynucleotide molecules were constructed as *Apa*I to *Xho*I fragments. The fragments were ligated into either the pAMG21-Fc N-terminal vector for the N-terminal orientation, or the pAMG21-Fc-C-terminal vector for the C-terminal orientation which had been previously digested with *Apa*LI and *Xho*I. The resulting ligation mixtures were transformed by electroporation into *E. coli* strain 2596 or 4167 cells (a *hsdR*- variant of strain 2596 cells) using standard procedures. Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having a correct nucleotide sequence. A single such clone was selected for each of the modified peptides.

Many of constructs were created using an alternative vector designated pAMG21-2xBs-N(*Zeo*R) Fc. This vector is similar to the above-described vector except that the vector digestion was performed with *Bsm*BI. Some constructs fused peptide sequences at both ends of the Fc. In those cases the vector was a composite of pAMG21-2xBs-N(*Zeo*R) Fc and pAMG21-2xBs-C-Fc.

Construction of pAMG21

Expression plasmid pAMG21 (ATCC No. 98113) is derived from expression vector pCFM1656 (ATCC No. 69576) and the expression vector system described in United States Patent No. 4,710,473, by following the procedure described in published International Patent Application WO 00/24782, all of which are incorporated herein by reference.

Fc N-terminal Vector

The Fc N-terminal vector was constructed using the pAMG21 Fc_Gly5_ Tpo vector as a template. A 5' PCR primer (below) was designed to remove the Tpo peptide sequence in pAMG Tpo Gly5 and replace it with a polylinker containing *Apa*LI and *Xho*I sites. Using this vector as a template, PCR was performed with Expand Long Polymerase, using the following 5' primer and a universal 3' primer:

5' primer: 5'-ACAAACAAACATATGGGTGCACAGAAAGCGGCCGCAAAAAA
CTCGAGGGTGGAGGCGGTGGGGACA-3' (Seq ID No: 297)

3' primer: 5'-GGTCATTACTGGACCGGATC-3' (Seq ID No: 298)

The resulting PCR product was gel purified and digested with restriction enzymes *NdeI* and *BsrGI*. Both the plasmid and the polynucleotide encoding the peptide of interest together with its linker were gel purified using Qiagen (Chatsworth, CA) gel purification spin columns. The plasmid and insert were then ligated using standard ligation procedures, and the resulting ligation mixture was transformed into *E. coli* cells (strain 2596). Single clones were selected and DNA sequencing was performed. A correct clone was identified and this was used as a vector source for the modified peptides described herein.

Construction of Fc C-terminal Vector

The Fc C-terminal vector was constructed using pAMG21 Fc_Gly5_Tpo vector as a template. A 3' PCR primer was designed to remove the Tpo peptide sequence and to replace it with a polylinker containing *ApaI* and *XhoI* sites. PCR was performed with Expand Long Polymerase using a universal 5' primer and the 3' primer.

5' Primer: 5'-CGTACAGGTTTACGCAAGAAAATGG-3' (Seq ID No: 299)

3' Primer: 5'-TTTGTGATCCATTACTCGAGTTTTTTTGC GGCCGCT
TTCTGTGACCACCACCTCCACCTTTAC-3' (Seq ID No: 300)

The resulting PCR product was gel purified and digested with restriction enzymes *BsrGI* and *BamHI*. Both the plasmid and the polynucleotide encoding each peptides of interest with its linker were gel purified via Qiagen gel purification spin columns. The plasmid and insert were then ligated using standard ligation procedures, and the resulting ligation mixture was transformed into *E. coli* (strain 2596) cells. Strain 2596 (ATCC # 202174) is a strain of *E. coli* K-12 modified to contain the lux promoter and two lambda temperature sensitive repressors, the *cI857s7* and the *lac I^Q* repressor. Single clones were selected and DNA sequencing was performed. A correct clone was identified and used as a source of each peptibody described herein.

Expression in *E. coli*.

Cultures of each of the pAMG21-Fc fusion constructs in *E. coli* strain 2596 were grown at 37°C in Terrific Broth medium (See Tartof and Hobbs, "Improved media for growing plasmid and cosmid clones", Bethesda Research Labs Focus, Volume 9, page 12, 1987, cited in aforementioned Sambrook et al. reference). Induction of gene product expression from the luxPR promoter was achieved following the addition of the synthetic autoinducer, N-(3-oxohexanoyl)-DL-homoserine lactone, to the culture medium to a final concentration of 20 nanograms per milliliter (ng/ml). Cultures were incubated at 37°C for an additional six hours. The bacterial cultures were then examined by microscopy for the presence of inclusion bodies and collected by

centrifugation. Refractile inclusion bodies were observed in induced cultures, indicating that the Fc-fusions were most likely produced in the insoluble fraction in *E. coli*. Cell pellets were lysed directly by resuspension in Laemmli sample buffer containing 10% β -mercaptoethanol and then analyzed by SDS-PAGE. In most cases, an intense coomassie-stained band of the appropriate molecular weight was observed on an SDS-PAGE gel.

Folding and purifying peptibodies

Cells were broken in water (1/10 volume per volume) by high pressure homogenization (3 passes at 15,000 PSI) and inclusion bodies were harvested by centrifugation (4000 RPM in J-6B for 30 minutes). Inclusion bodies were solubilized in 6 M guanidine, 50 mM Tris, 8 mM DTT, pH 8.0 for 1 hour at a 1/10 ratio at ambient temperature. The solubilized mixture was diluted 25 times into 4 M urea, 20% glycerol, 50 mM Tris, 160 mM arginine, 3 mM cysteine, 1 mM cystamine, pH 8.5. The mixture was incubated overnight in the cold. The mixture was then dialyzed against 10 mM Tris pH 8.5, 50 mM NaCl, 1.5 M urea. After an overnight dialysis the pH of the dialysate was adjusted to pH 5 with acetic acid. The precipitate was removed by centrifugation and the supernatant was loaded onto a SP-Sepharose Fast Flow column equilibrated in 10 mM NaAc, 50 mM NaCl, pH 5, 4°C). After loading the column was washed to baseline with 10 mM NaAc, 50 mM NaCl, pH 5.2. The column was developed with a 20 column volume gradient from 50mM -500 mM NaCl in the acetate buffer. Alternatively, after the wash to baseline, the column was washed with 5 column volumes of 10 mM sodium phosphate pH 7.0 and the column developed with a 15 column volume gradient from 0-400 mM NaCl in phosphate buffer. Column fractions were analyzed by SDS-PAGE. Fractions containing dimeric peptibody were pooled. Fractions were also analyzed by gel filtration to determine if any aggregate was present.

A number of peptibodies were prepared from the peptides of Table I. The peptides were attached to the human IgG1 Fc molecule to form the peptibodies in Table II. Regarding the peptibodies in Table II, the C configuration indicates that the peptide named was attached at the C-termini of the Fc. The N configuration indicates that the peptide named was attached at the N-termini of the Fc. The N,C configuration indicates that one peptide was attached at the N-termini and one at the C-termini of each Fc molecule. The 2x designation indicates that the two peptides named were attached in tandem to each other and also attached at the N or the C termini, or both the N,C of the Fc, separated by the linker indicated. Two peptides attached in tandem separated by a linker, are indicated, for example, as Myostatin-TN8-29-19-8g, which indicates that TN8-29 peptide is attached via a (gly)₈ linker to TN8-19 peptide. The peptide(s) were attached to the Fc via a (gly)₅ linker sequence unless otherwise specified. In some instances the peptide(s) were attached via a k linker. The linker designated k or 1k refers to the gsgsatggsgstassgsgsatg (Seq ID

No: 301) linker sequence, with kc referring to the linker attached to the C-terminus of the Fc, and kn referring to the linker attached to the N-terminus of the Fc. In Table II below, column 4 refers to the linker sequence connecting the Fc to the first peptide and the fifth column refers to the configuration N or C or both.

- 5 Since the Fc molecule dimerizes in solution, a peptibody constructed so as to have one peptide will actually be a dimer with two copies of the peptide and two Fc molecules, and the 2X version having two peptides in tandem will actually be a dimer with four copies of the peptide and two Fc molecules.

10 Since the peptibodies given in Table II are expressed in *E. coli*, the first amino acid residue is Met (M). Therefore, the peptibodies in the N configuration are Met-peptide-linker-Fc, or Met-peptide-linker-peptide-linker-Fc, for example. Peptibodies in the C configuration are arranged as Met-Fc-linker-peptide or Met-Fc-linker-peptide-linker-peptide, for example. Peptibodies in the C,N configuration are a combination of both, for example, Met-peptide-linker-Fc-linker-peptide.

- 15 Nucleotide sequences encoding exemplary peptibodies are provided below in Table II. The polynucleotide sequences encoding an exemplary peptibody of the present invention includes a nucleotide sequence encoding the Fc polypeptide sequence such as the following:

5'-GACAAACTCACACATGTCCACCTTGCCCAGCACCTGAACTC
 CTGGGGGGACCGTCAGTTTTCTCTTCCCCCAAACCCAAGGACACCCTCA
 20 TGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACG
 AAGACCCTGAGGTCAAGTTCAACTGCTACGTGGACGGCGTGGAGGTGCATA
 ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTG
 GTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
 AAGTGCAAGGTCTCCAACAAAGCCCTCCAGCCCCCATCGAGAAAACCATC
 25 TCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCA
 TCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAA
 GGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
 GAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCT
 TCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACG
 30 TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAA
 GAGCCTCTCCCTGTCTCCGGGTAAA-3' (Seq ID No: 301)

In addition, the polynucleotides encoding the ggggg linker such as the following are included:

- 35 5'-GGTGGAGGTGGTGGT-3' (Seq ID No: 302)

The polynucleotide encoding the peptibody also includes the codon encoding the methionine ATG and a stop codon such as TAA.

Therefore, the structure of the first peptibody in Table II is TN8-Con1 with a C configuration and a (gly)₅ linker is as follows: M-Fc-GGGGG-KDKCKMWHWMCKPP (Seq ID No: 303).

Exemplary polynucleotides encoding this peptibody would be:

5'- ATGGACAAACTCACACATGTCCACCTTGCCCAGCACCTGAA
 CTCCTGGGGGGACCGTCAGTTTTCTCTTCCCCCAAACCCAAGGACACCC
 TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCC
 ACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC
 ATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGT
 GTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAG
 TACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACC
 ATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC
 CCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTC
 AAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
 CCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC
 TTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG
 AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGC
 AGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGTGGAGGTGGTGGTAAGACAA
 ATGCAAAATGTGGCACTGGATGTGCAAACCGCCG-3' (Seq ID No: 304)

TABLE II

| Peptibody Name | Peptide | Nucleotide Sequence (Seq ID No) | | |
|--------------------|----------------|--|-------|---|
| Myostatin-TN8-con1 | KDKCKMWHWMCKPP | AAAGACAAATGCAAAATGTGGCACTG GATGTGCAAACCGCCG (Seq. ID No: 147) | 5 gly | C |
| Myostatin-TN8-con2 | KDLCAMWHWMCKPP | AAAGACCTGTGCGCTATGTGGCACTG GATGTGCAAACCGCCG (Seq. ID No: 148) | 5 gly | C |
| Myostatin-TN8-con3 | KDLCKMWKWMCKPP | AAAGACCTGTGCAAAATGTGGAAATG GATGTGCAAACCGCCG (Seq ID No: 149) | 5 gly | C |
| Myostatin-TN8-con4 | KDLCKMWHWMCKPK | AAAGACCTGTGCAAAATGTGGCACTG GATGTGCAAACCGAAA (Seq ID No: 150) | 5 gly | C |
| Myostatin-TN8-con5 | WYPCYEFHFWCYDL | TGGTACCCGTGCTACGAATTCCACTTC TGGTGCTACGACCTG (Seq ID No: 151) | 5 gly | C |
| Myostatin-TN8-con5 | WYPCYEFHFWCYDL | TGGTACCCGTGCTACGAATTCCACTTC TGGTGCTACGACCTG (Seq ID No: 152) | 5 gly | N |
| Myostatin-TN8-con6 | WYPCYEGHFWCYDL | TGGTACCCGTGCTACGAAGGTCATT CTGGTGCTACGACCTG (Seq ID No: 153) | 5 gly | C |
| Myostatin-TN8-con6 | WYPCYEGHFWCYDL | TGGTACCCGTGCTACGAAGGTCATT CTGGTGCTACGACCTG (Seq ID No: 154) | 5 gly | N |
| Myostatin-TN8-con7 | IFGCKWWDVQCYQF | ATCTTCGGTTGCAAATGGTGGGACGT TCAGTGCTACCAGTTC (Seq ID No: 155) | 5 gly | C |
| Myostatin-TN8-con8 | IFGCKWWDVDCYQF | ATCTTCGGTTGCAAATGGTGGGACGT TGACTGCTACCAGTTC (Seq ID No: 156) | 5 gly | C |
| Myostatin-TN8-con8 | IFGCKWWDVDCYQF | ATCTTCGGTTGCAAATGGTGGGACGT TGACTGCTACCAGTTC (Seq ID No: 157) | 5 gly | N |
| Myostatin-TN8- | ADWCVSPNWFCMVM | GCTGACTGGTGCGTTTCCCCGAACCTG | 5 gly | C |

| | | | | |
|---------------------|----------------|--|-------|---|
| con9 | | GTTCTGCATGGTTATG (Seq ID No: 158) | | |
| Myostatin-TN8-con10 | HKFCPWWALFCWDF | CACAAATTCTGCCCCGTGGTGGGCTCT GTTCTGCTGGGACTTC (Seq ID No: 159) | 5 gly | C |
| Myostatin-TN8-1 | KDLCKMWHWMCKPP | AAAGACCTGTGCAAATGTGGCACTG GATGTGCAAACCGCCG (Seq ID No: 160) | 5 gly | C |
| Myostatin-TN8-2 | IDKCAIWGWMCPPL | ATCGACAAATGCGCTATCTGGGGTTG GATGTGCCCCGCCGCTG (Seq ID No: 161) | 5 gly | C |
| Myostatin-TN8-3 | WYPCGEFGMWCLNV | TGGTACCCGTGCGGTGAATTCGGTAT GTGGTGCTGAACGTT (Seq ID No: 162) | 5 gly | C |
| Myostatin-TN8-4 | WFTCLWNCNE | TGGTTCACCTGCCTGTGGAAGTGC CAACGAA (Seq ID No: 163) | 5 gly | C |
| Myostatin-TN8-5 | HTPCPWFAPLCVEW | CACACCCCGTGCCCCGTGGTTCGCTCC GCTGTGCGTTGAATGG (Seq ID No: 164) | 5 gly | C |
| Myostatin-TN8-6 | KEWCWRWKWMCKPE | AAAGAATGGTGCTGGCGTTGGAAATG GATGTGCAAACCGGAA (Seq ID No: 165) | 5 gly | C |
| Myostatin-TN8-7 | FETCPSWAYFCLDI | TTCGAAACCTGCCCCGTCTGGGCTTA CTTCTGCCTGGACATC (Seq ID No: 166) | 5 gly | C |
| Myostatin-TN8-7 | FETCPSWAYFCLDI | TTCGAAACCTGCCCCGTCTGGGCTTA CTTCTGCCTGGACATC (Seq ID No: 167) | 5 gly | N |
| Myostatin-TN8-8 | AYKCEANDWGCWWL | GCTTACAAATGCGAAGCTAACGACTG GGGTTGCTGGTGGCTG (Seq ID No: 168) | 5 gly | C |
| Myostatin-TN8-9 | NSWCEDQWHRCWWL | AACTCCTGGTGCGAAGACCAGTGGCA CCGTTGCTGGTGGCTG (Seq ID No: 169) | 5 gly | C |
| Myostatin-TN8-10 | WSACYAGHFWCYDL | TGGTCCGCTTGCTACGCTGGTCACTTC TGGTGCTACGACCTG (Seq ID No: 170) | 5 gly | C |
| Myostatin-TN8-11 | ANWCVSPNWFVM | GCTAACTGGTGCGTTTCCCCGAAGT GTTCTGCATGGTTATG (Seq ID No: 171) | 5 gly | C |
| Myostatin-TN8-12 | WTECYQQEFWCWNL | TGGACCGAATGCTACCAGCAGGAATT CTGGTGCTGGAACCTG (Seq ID No: 172) | 5 gly | C |
| Myostatin-TN8-13 | ENTCERWKWMCPPK | GAAAACACCTGCGAACGTTGGAAATG GATGTGCCCCGCCGAAA (Seq ID No: 173) | 5 gly | C |
| Myostatin-TN8-14 | WLPCHQEGFWCMNF | TGGCTGCCGTGCCACCAGGAAGGTTT CTGGTGCTGAAGTTC (Seq ID No: 174) | 5 gly | C |
| Myostatin-TN8-15 | STMCSQWHWMCNPF | TCCACCATGTGCTCCCAGTGGCACTG GATGTGCAACCCGTTT (Seq ID No: 175) | 5 gly | C |
| Myostatin-TN8-16 | IFGCHWWDVDCYQF | ATCTTCGGTTGCCACTGGTGGGACGT TGACTGCTACCAGTTC (Seq ID No: 176) | 5 gly | C |
| Myostatin-TN8-17 | IYGCKWWDIQCIDI | ATCTACGGTTGCAAATGGTGGGACAT CCAGTGCTACGACATC (Seq ID No: 177) | 5 gly | C |
| Myostatin-TN8-18 | PDWCIDPDWWCKFW | CCGGACTGGTGCATCGATCCGGACTG GTGGTGCAAATTCTGG (Seq ID No: 178) | 5 gly | C |
| Myostatin-TN8-19 | QGHCTRWPWMCPPY | CAGGGTCACTGCACCCGTTGGCCGTG GATGTGCCCCCGGTAC (Seq ID No: 179) | 5 gly | C |
| Myostatin-TN8-20 | WQECYREGFWCLQT | TGGCAGGAATGCTACCGTGAAGGTTT CTGGTGCTGCAGACC (Seq ID No: 180) | 5 gly | C |

| | | | | |
|------------------|----------------|--|-------|---|
| Myostatin-TN8-21 | WFDCYGPFGKCWSP | TGGTTCGACTGCTACGGTCCGGGTTTC AAATGCTGGTCCCCG (Seq ID No: 181) | 5 gly | C |
| Myostatin-TN8-22 | GVRCPKGHLWCLYP | GGTGTTCGTTGCCCGAAAGGTCACCT GTGGTGCCTGTACCCG (Seq ID No: 182) | 5 gly | C |
| Myostatin-TN8-23 | HWACGYWPWSCWV | CACTGGGCTTGCGGTTACTGGCCGTG GTCCTGCAAATGGGTT (Seq ID No: 183) | 5 gly | C |
| Myostatin-TN8-24 | GPACHSPWWCVFG | GGTCCGGCTTGCCACTCCCCGTGGTG GTGGTGCCTTTTCGGT (Seq ID No: 184) | 5 gly | C |
| Myostatin-TN8-25 | TTWCISPMWFCSQQ | ACCACCTGGTGCATCTCCCCGATGTG GTTCTGCTCCCAGCAG (Seq ID No: 185) | 5 gly | C |
| Myostatin-TN8-26 | HKFCPPWAIFCWDF | CACAAATTCTGCCC GCCGTGGGCTAT CTTCTGCTGGGACTTC (Seq ID No: 186) | 5 gly | N |
| Myostatin-TN8-27 | PDWCVSPRWYCNMW | CCGGACTGGTGCCTTCCCCGCGTTG GTACTGCAACATGTGG (Seq ID No: 187) | 5 gly | N |
| Myostatin-TN8-28 | VWKCHWFGMDCEPT | GTTTGGAAATGCCACTGGTTCGGTAT GGACTGCGAACCGACC (Seq ID No: 188) | 5 gly | N |
| Myostatin-TN8-29 | KKHCQIWTWMCAPK | AAAAA AACTGCCAGATCTGGACCTG GATGTGCGCTCCGAAA (Seq ID No: 189) | 5 gly | N |
| Myostatin-TN8-30 | WFQCGSTLFWCYNL | TGGTTCAGTGCGGTTCCACCCTGTTC TGGTGCTACAACCTG (Seq ID No: 190) | 5 gly | N |
| Myostatin-TN8-31 | WSPCYDHYFYCYTI | TGGTCCCCGTGCTACGACCACTACTTC TACTGCTACACCATC (Seq ID No: 191) | 5 gly | N |
| Myostatin-TN8-32 | SWMCGFFKEVCMWV | TCCTGGATGTGCGGTTTCTTCAAAGA AGTTTGATGTGGGTT (Seq ID No: 192) | 5 gly | N |
| Myostatin-TN8-33 | EMLCMIHPVFCNPH | GAAATGCTGTGCATGATCCACCCGGT TTTCTGCAACCCGCAC (Seq ID No: 193) | 5 gly | N |
| Myostatin-TN8-34 | LKTCNLWPWMCPL | CTGAAAACCTGCAACCTGTGGCCGTG GATGTGCCCCGCCGCTG (Seq ID No: 194) | 5 gly | N |
| Myostatin-TN8-35 | VVGCKWYEAWCYNK | GTTGTTGGTTGCAAATGGTACGAAGC TTGGTGCTACAACAAA (Seq ID No: 195) | 5 gly | N |
| Myostatin-TN8-36 | PIHCTQAWWMCPTT | CCGATCCACTGCACCCAGTGGGCTTG GATGTGCCCCGCCGACC (Seq ID No: 196) | 5 gly | N |
| Myostatin-TN8-37 | DSNCPWYFLSCVIF | GACTCCAAGTCCCCGTGGTACTTCCT GTCCTGCGTTATCTTC (Seq ID No: 197) | 5 gly | N |
| Myostatin-TN8-38 | HIWCNLAMMKCVEM | CACATCTGGTGCAACCTGGCTATGAT GAAATGCGTTGAAATG (Seq ID No: 198) | 5 gly | N |
| Myostatin-TN8-39 | NLQCIYFLGKCIYF | AACCTGCAGTGCATCTACTTCCTGGG TAAATGCATCTACTTC (Seq ID No: 199) | 5 gly | N |
| Myostatin-TN8-40 | AWRCMWFSDVCTPG | GCTTGGCGTTGCATGTGGTTCTCCGAC GTTTGCACCCCGGGT (Seq ID No: 200) | 5 gly | N |
| Myostatin-TN8-41 | WFRCLDADWCTSV | TGGTTTCGTTGTTTCTTGATGCTGAT TGGTGTACTTCTGTT (Seq ID No: 201) | 5 gly | N |
| Myostatin-TN8-42 | EKICQMWSWMCAPP | GAAAAAATTTGTCAAATGTGGTCTTG GATGTGTGCTCCACCA (Seq ID No: 202) | 5 gly | N |
| Myostatin-TN8-43 | WFYCHLNKSECTEP | TGGTTTTATTGTCATCTTAATAAATCT | 5 gly | N |

| | | | | |
|-------------------|------------------------|--|-------|---|
| | | GAATGTACTGAACCA (Seq ID No: 203) | | |
| Myostatin-TN8-44 | FWRCAIGIDKCKRV | TTTGGCGTTGTGCTATTGGTATTGAT AAATGTAAACGTGTT (Seq ID No: 204) | 5 gly | N |
| Myostatin-TN8-45 | NLGCKWYEVWCFTY | AATCTTGGTTGTAAATGGTATGAAGT TTGGTGTTTTACTTAT (Seq ID No: 205) | 5 gly | N |
| Myostatin-TN8-46 | IDLNMWDGMCYPP | ATTGATCTTTGTAATATGTGGGATGGT ATGTGTTATCCACCA (Seq ID No: 206) | 5 gly | N |
| Myostatin-TN8-47 | EMPCNIWGWMCPPV | GAAATGCCATGTAATATTTGGGGTTG GATGTGTCCACCAGTT (Seq ID No: 207) | 5 gly | N |
| Myostatin-TN12-1 | WFRCVLTGIVDWSECF GL | TGGTTCCGTTGCGTTCTGACCGGTATC GTTGACTGGTCCGAATGCTTCGGTCT G (Seq ID No: 208) | 5 gly | N |
| Myostatin-TN12-2 | GFSCFGLDEFYVDCSP F | GGTTTCTCCTGCACCTTCGGTCTGGAC GAATTCTACGTTGACTGCTCCCCGTTT (Seq ID No: 209) | 5 gly | N |
| Myostatin-TN12-3 | LPWCHDQVNADWGFC MLW | CTGCCGTGGTGCCACGACCAGGTTAA CGCTGACTGGGGTTTCTGCATGCTGT GG (Seq ID No: 210) | 5 gly | N |
| Myostatin-TN12-4 | YPTCSEKFWIYGQTCV LW | TACCCGACCTGCTCCGAAAAATTCTG GATCTACGGTCAGACCTGCGTTCTGT GG (Seq ID No: 211) | 5 gly | N |
| Myostatin-TN12-5 | LGPCPIHHGPWPQYCV YW | CTGGGTCCGTGCCCCGATCCACCACGG TCCGTGGCCGCAGTACTGCGTTTACT GG (Seq ID No: 212) | 5 gly | N |
| Myostatin-TN12-6 | PFPCEHQISWLGHCLS F | CCGTTCCCGTGCGAAACCCACCAGAT CTCCTGGCTGGGTCACTGCCTGTCCTT C (Seq ID No: 213) | 5 gly | N |
| Myostatin-TN12-7 | HWGCEDLMWSWHPLC RRP | CACTGGGGTTGCGAAGACCTGATGTG GTCCTGGCACCCGCTGTGCCGTCGTC CG (Seq ID No: 214) | 5 gly | N |
| Myostatin-TN12-8 | LPLCDADMMPTIGFCV AY | CTGCCGCTGTGCGACGCTGACATGAT GCCGACCATCGGTTTCTGCGTTGCTTA C (Seq ID No: 215) | 5 gly | N |
| Myostatin-TN12-9 | SHWCETTFWMNYAKC VHA | TCCCACTGGTGCGAAACCACCTTCTG GATGAACTACGCTAAATGCGTTCACG CT (Seq ID No: 216) | 5 gly | N |
| Myostatin-TN12-10 | LPKCTHVFPDQGGFCL WY | CTGCCGAAATGCACCCACGTTCCGTT CGACCAGGGTGGTTTCTGCCTGTGGT AC (Seq ID No: 217) | 5 gly | N |
| Myostatin-TN12-11 | FSSCWSPVSRQDMFCV FY | TTCTCCTCCTGCTGGTCCCCGGTTTCC CGTCAGGACATGTTCTGCGTTTCTAC (Seq ID No: 218) | 5 gly | N |
| Myostatin-TN12-13 | SHKCEYSGWLQPLCYR P | TCCCAAAATGCGAATACTCCGGTTG GCTGCAGCCGCTGTGCTACCGTCCG (Seq ID No: 219) | 5 gly | N |
| Myostatin-TN12-14 | PWWCQDNVYQHMLH CDSP | CCGTGGTGGTGCCAGGACAACTACGT TCAGCACATGCTGCACTGCGACTCCC CG (Seq ID No: 220) | 5 gly | N |
| Myostatin-TN12-15 | WFRCLMNSFDAFQC VSY | TGGTTCCGTTGCATGCTGATGAACTCC TTCGACGCTTTCAGTGCGTTTCTAC (Seq ID No: 221) | 5 gly | N |
| Myostatin-TN12-16 | PDACRDQPWYMFMG MLG | CCGACGCTTGCCGTGACCAGCCGTG GTACATGTTTCATGGGTTGCATGCTGG GT (Seq ID No: 222) | 5 gly | N |
| Myostatin-TN12- | FLACFVEFELCFDS | TTCTGCGCTTGCTTCGTTGAATTCGAA | 5 gly | N |

| | | | | |
|-------------------|---------------------|---|-------|--------|
| 17 | | CTGTGCTTCGACTCC (Seq ID No: 223) | | |
| Myostatin-TN12-18 | SAYCIITESDPYVLCVPL | TCCGCTTACTGCATCATCACCGAATCCGACCCGTACGTTCTGTGCGTTCCGCTG (Seq ID No: 224) | 5 gly | N |
| Myostatin-TN12-19 | PSICESYSTMWLPMCQHN | CCGTCCATCTGCGAATCCTACTCCACCATGTGGCTGCCGATGTGCCAGCACAA C (Seq ID No: 225) | 5 gly | N |
| Myostatin-TN12-20 | WLDCHDDSWAWTKMCRSH | TGGCTGGACTGCCACGACGACTCCTGGGCTTGACCAAAATGTGCCGTTCCC AC (Seq ID No: 226) | 5 gly | N |
| Myostatin-TN12-21 | YLNCVMMNTSPFVECVFN | TACCTGAACTGCGTTATGATGAACACCTCCCCGTTGTTGAATGCGTTTTCAA C (Seq ID No: 227) | 5 gly | N |
| Myostatin-TN12-22 | YPWCDGFMIQQGITCMFY | TACCCGTGGTGCGACGGTTTCATGATCCAGCAGGGTATCACCTGCATGTTCT AC (Seq ID No: 228) | 5 gly | N |
| Myostatin-TN12-23 | FDYCTWLNGFKDWKCSR | TTCGACTACTGCACCTGGCTGAACGGTTTCAAAGACTGGAAATGCTGGTCCC GT (Seq ID No: 229) | 5 gly | N |
| Myostatin-TN12-24 | LPLCNLKEISHVQACVLF | CTGCCGCTGTGCAACCTGAAAGAAATCTCCACGTTGAGGCTTGCGTTCTGTT C (Seq ID No: 230) | 5 gly | N |
| Myostatin-TN12-25 | SPECAFARWLGIEQCQRD | TCCCCGGAATGCGCTTTCGCTCGTTGGCTGGGTATCGAACAGTGCCAGCGTGA C (Seq ID No: 231) | 5 gly | N |
| Myostatin-TN12-26 | YPQCFNLHLEWTECDWF | TACCCGCAGTGCTTCAACCTGCACCTGCTGGAATGGACCGAATGCGACTGGT TC (Seq ID No: 232) | 5 gly | N |
| Myostatin-TN12-27 | RWRCEIYDSEFLPKCWFF | CGTTGGCGTTGCGAAATCTACGACTCCGAATTCCTGCCGAAATGCTGGTTCTT C (Seq ID No: 233) | 5 gly | N |
| Myostatin-TN12-28 | LVGCDNVWHRCKLF | CTGGTTGGTTGCGACAACGTTTGGCA CCGTTGCAAACGTGTT (Seq ID No: 234) | 5 gly | N |
| Myostatin-TN12-29 | AGWCHVWGEMFGMGCSAL | GCTGGTTGGTGCCACGTTTGGGGTGA AATGTTGCGTATGGGTTGCTCCGCTCT G (Seq ID No: 235) | 5 gly | N |
| Myostatin-TN12-30 | HHECEWMARWMSLD CVGL | CACCACGAATGCGAATGGATGGCTCG TTGGATGTCCCTGGACTGCGTTGGTCT G (Seq ID No: 236) | 5 gly | N |
| Myostatin-TN12-31 | FPMCGLIAGMKDFDFCVWY | TTCCCGATGTGCGGTATCGCTGGTAT GAAAGACTTCGACTTCTGCGTTTGGT AC (Seq ID No: 237) | 5 gly | N |
| Myostatin-TN12-32 | RDDCTFWPEWLWKLCERP | CGTGATGATTGTACTTTTTGGCCAGAA TGGCTTTGGAACTTTGTGAACGTCC A (Seq ID No: 238) | 5 gly | N |
| Myostatin-TN12-33 | YNFCSYLFVGSKEACQLP | TATAATTTTTGTTCTTATCTTTTTGGTG TTTCTAAAGAAGCTTGCAACTTCCA (Seq ID No: 239) | 5 gly | N |
| Myostatin-TN12-34 | AHWCEQGPWRYGNICMAY | GCTCATTGGTGTGAACAAGGTCCATG CCGTTATGGTAATATTTGTATGGCTTA T (Seq ID No: 240) | 5 gly | N C |
| Myostatin-TN12-35 | NLVCGKISAWGDEACARA | AATCTTGTGTGGTAAAATTTCTGCT TGGGGTGATGAAGCTTGTGCTCGTGCT T (Seq ID No: 241) | 5 gly | N |
| Myostatin-TN12- | HNVCTIMGSPMKWFC | CATAATGTTTGTACTATTATGGGTCCA | 5 gly | N |

| | | | | |
|---------------------|--------------------------|--|-------|--------|
| 36 | WND | TCTATGAAATGGTTTTGTTGGAATGAT (Seq ID No: 242) | | C |
| Myostatin-TN12-37 | NDLCAMWGWRTIWC QNS | AATGATCTTTGTGCTATGTGGGGTTGG CGTAATACTATTTGGTGTCAAATTCT (Seq ID No: 243) | 5 gly | N C |
| Myostatin-TN12-38 | PPFCQNDNDMLQSLCK LL | CCACCATTTTGTCAAAATGATAATGA TATGCTTCAATCTCTTTGTAAACTTCT T (Seq ID No: 244) | 5 gly | N |
| Myostatin-TN12-39 | WYDCNVPNELLSGLCR LF | TGGTATGATTGTAATGTTCCAAATGA ACTTCTTTCTGGTCTTTGTCTCTTTTT (Seq ID No: 245) | 5 gly | N |
| Myostatin-TN12-40 | YGDCDQNHWMWPFTC LSL | TATGGTGATTGTGATCAAAATCATTG GATGTGGCCATTTACTTGTCTTTCTCT T (Seq ID No: 246) | 5 gly | N C |
| Myostatin-TN12-41 | GWMCHFDLHDWGAT CQPD | GGTTGGATGTGTCATTTTGATCTTCAT GATTGGGGTGCTACTTGTCAACCAGA T (Seq ID No: 247) | 5 gly | N |
| Myostatin-TN12-42 | YFHCMPGGHEFEVHCE SF | TATTTTCATTGTATGTTTGGTGGTCAT GAATTTGAAGTTCATTGTGAATCTTTT (Seq ID No: 248) | 5 gly | N C |
| Myostatin-TN12-43 | AYWCWHGQCVR | GCTTATTGGTGTGGCATGGTCAATGT GTTCTGTTT (Seq ID No: 249) | 5 gly | N |
| Myostatin-Linear-1 | SEHWTFTDWDGNEW WVRPF | TCCGAACACTGGACCTTCACCGACTG GGACGGTAACGAATGGTGGGTTTCGTC CGTTC (Seq ID No: 250) | 5 gly | N |
| Myostatin-Linear-2 | MEMLDSLFECLKDMVP ISKA | ATGGAAATGCTGGACTCCCTGTTTCCA ACTGCTGAAAGACATGGTTCGGATCT CCAAAGCT (Seq ID No: 251) | 5 gly | N |
| Myostatin-Linear-3 | SPPEALMEWLGWQY GKFT | TCCCCGCCGGAAGAAGCTCTGATGGA ATGGCTGGGTTGGCAGTACGGTAAAT TCACC (Seq ID No: 252) | 5 gly | N |
| Myostatin-Linear-4 | SPENLLNDLYILMTKQ EWYG | TCCCCGGAACCTGCTGAACGACCT GTACATCCTGATGACCAAACAGGAAT GGTACGGT (Seq ID No: 253) | 5 gly | N |
| Myostatin-Linear-5 | FHWEEGIPFHVTPYS YDRM | TTCCACTGGGAAGAAGGTATCCCGTT CCACGTTGTTACCCCGTACTCTACGA CCGTATG (Seq ID No: 254) | 5 gly | N |
| Myostatin-Linear-6 | KRLLEQFMNDLAEVLS GHS | AAACGTCTGCTGGAACAGTTCATGAA CGACCTGGCTGAACTGGTTCCGGTC ACTCC (Seq ID No: 255) | 5 gly | N |
| Myostatin-Linear-7 | DTRDALFQEFYEFVRS RLVI | GACACCCGTGACGCTCTGTTCCAGGA ATTCTACGAATTCGTTCTGTTCCCGTCT GGTTATC (Seq ID No: 256) | 5 gly | N |
| Myostatin-Linear-8 | RMSAAPRPLTYRDIMD QYWH | CGTATGTCCGCTGCTCCGCTCCGCTG ACCTACCGTGACATCATGGACCAGTA CTGGCAC (Seq ID No: 257) | 5 gly | N |
| Myostatin-Linear-9 | NDKAHFFEMFMFDVH NFVES | AACGACAAAGCTCACTTCTTCGAAAT GTTTCATGTTGACGTTTCAAACTTCGT TGAATCC (Seq ID No: 258) | 5 gly | N |
| Myostatin-Linear-10 | QTQAQKIDGLWELLQS IRNQ | CAGACCCAGGCTCAGAAAATCGACGG TCTGTGGGAAGTCTGCAGTCCATCC GTAACCAG (Seq ID No: 259) | 5 gly | N |
| Myostatin-Linear-11 | MLSEFEEFLGNLVHRQ EA | ATGCTGTCCGAATTCGAAGAATTCCT GGGTAACCTGGTTACCGTCAGGAAG CT (Seq ID No: 260) | 5 gly | N |
| Myostatin-Linear- | YTPKMGSEWTSFWHN | TACACCCCGAAAATGGGTTCGGAATG | 5 gly | N |

| | | | | |
|---------------------|---------------------------|--|-------|--------|
| 12 | RIHYL | GACCTCCTTCTGGCACAACCGTATCC ACTACCTG (Seq ID No: 261) | | |
| Myostatin-Linear-13 | LNDTLLRELKMVLNSL SDMK | CTGAACGACACCCTGCTGCGTGAAC GAAAATGGTTCTGAACTCCCTGTCCG ACATGAAA (Seq ID No: 262) | 5 gly | N |
| Myostatin-Linear-14 | FDVERDLMRWLEGFM QSAAT | TTCGACGTTGAACGTGACCTGATGCG TTGGCTGGAAGGTTTCATGCAGTCCG CTGCTACC (Seq ID No: 263) | 5 gly | N |
| Myostatin-Linear-15 | HHGWNLYLRKGSAPQW FEAWV | CACCACGGTTGGAACCTACCTGCGTAA AGGTTCCGCTCCGCAGTGGTTCGAAG CTTGGGTT (Seq ID No: 264) | 5 gly | N |
| Myostatin-Linear-16 | VESLHQLQMWLDQKL ASGPH | GTTGAATCCCTGCACCAGCTGCAGAT GTGGCTGGACCAGAACTGGCTTCCG GTCCGCAC (Seq ID No: 265) | 5 gly | N |
| Myostatin-Linear-17 | RATLLKDFWQLVEGY GDN | CGTGCTACCCTGCTGAAAGACTTCTG GCAGCTGGTTGAAGGTTACGGTGACA AC (Seq ID No: 266) | 5 gly | N |
| Myostatin-Linear-18 | EELLREFYRFVSAFDY | GAAGAACTGCTGCGTGAATTCTACCG TTTCGTTTCCGCTTTCGACTAC (Seq ID No: 267) | 5 gly | N |
| Myostatin-Linear-19 | GLLDEFSHFIAEQFYQ MPGG | GGTCTGCTGGACGAATTCTCCCACTTC ATCGCTGAACAGTTCTACCAGATGCC GGGTGGT (Seq ID No: 268) | 5 gly | N |
| Myostatin-Linear-20 | YREMSMLEGLLDVLER LQHY | TACCGTGAAATGTCCATGCTGGAAGG TCTGCTGGACGTTCTGGAACGTCTGC AGCACTAC (Seq ID No: 269) | 5 gly | N |
| Myostatin-Linear-21 | HNSSQMLLSELIMLVG SMMQ | CACAACTCCTCCCAGATGCTGCTGTC CGAACTGATCATGCTGGTTGGTTCCA TGATGCAG (Seq ID No: 270) | 5 gly | N |
| Myostatin-Linear-22 | WREHFLNSDYIRDCLI AIDG | TGGCGTGAACACTTCTGAACTCCGA TCACATCCGTGACAACTGATCGCTA TCGACGGT (Seq ID No: 271) | 5 gly | N |
| Myostatin-Linear-23 | QFPFYVFDDLPAQLEY WIA | CAGTTCCCGTTCTACGTTTTTCGACGAC CTGCCGGCTCAGCTGGAATACTGGAT CGCT (Seq ID No: 272) | 5 gly | N |
| Myostatin-Linear-24 | EFFHWLHNHRSEVNH WLDMN | GAATTCTTCCACTGGCTGCACAACCA CCGTTCCGAAGTTAACCACTGGCTGG ACATGAAC (Seq ID No: 273) | 5 gly | N |
| Myostatin-Linear-25 | EALFQNFFRDVLTLSER EY | GAAGCTCTTTTCAAATTTTTTTCGT GATGTTCTTACTCTTCTGAACGTGAA TAT (Seq ID No: 274) | 5 gly | N C |
| Myostatin-Linear-26 | QYWEQQWMTYFRENG LHVQY | CAATATTGGGAACAACAATGGATGAC TTATTTTCGTGAAAATGGTCTTCATGT TCAATAT (Seq ID No: 275) | 5 gly | N |
| Myostatin-Linear-27 | NQRMMLDLWRIMTP MFGRS | AATCAACGTATGATGCTTGAAGATCT TTGGCGTATTGACTCCAATGTTTGG TCGTTCT (Seq ID No: 276) | 5 gly | N C |
| Myostatin-Linear-29 | FLDELKAELSRHYALD DLDE | TTTCTTGATGAACCTAAAGCTGAACTT TCTCGTCATTATGCTCTTGATGATCTT GATGAA (Seq ID No: 277) | 5 gly | N |
| Myostatin-Linear-30 | GKLIEGLLNELMQLET MPD | GGTAAACTTATTGAAGGCTTCTTAAT GAACTTATGCAACTTGAACTTTTATG CCAGAT (Seq ID No: 278) | 5 gly | N C |
| Myostatin-Linear-31 | ILLDEYKKDWSWF | ATTCTTCTTCTTGATGAATATAAAAAA GATTGGAAATCTTGGTTT (Seq ID No: 279) | 5 gly | N |

| | | | | |
|----------------------------|---|---|-------|---|
| Myostatin- 2XTN8-19 kc | QGHCTRWPWMCPPYG SGSATGGSGSTASSGSG SATGQGHCTRWPWMC PPY | CAGGGCCACTGTACTCGCTGGCCGTG GATGTGCCCCCGGTACGGTTCTGGTT CCGCTACCGGTGGTTCTGGTTCCACTG CTTCTTCTGGTTCCGGTTCTGCTACTG GTCAGGGTCACTGCACTCGTTGGCCA TGGATGTGTCCACCGTAT (Seq ID No: 280) | 1k | N |
| Myostatin- 2XTN8-CON6 | WYPCYEGHFWCYDLG SGSTASSGSGSATGWY PCYEGHFWCYDL | TGGTATCCGTGTTATGAGGGTCACTTC TGGTGCTACGATCTGGGTCTGGTTCC ACTGCTTCTTCTGGTTCCGGTTCCGCT ACTGGTTGGTACCCGTGCTACGAAGG TCACTTTTGGTGTTATGATCTG (Seq ID No: 281) | 5 gly | C |
| Myostatin- 2XTN8-5 kc | HTPCPWFAPLCVEWGS GSATGGSGSTASSGSG ATGHTPCPWFAPLCVE W | CACACTCCGTGTCCGTGGTTTGCTCCG CTGTGCGTTGAATGGGGTTCTGGTTCC GCTACTGGTGGTTCCGGTTCCACTGCT TCTTCTGGTTCCGGTTCTGCAACTGGT CACACCCCGTGCCCGTGGTTTGACCC GCTGTGTGTAGAGTGG (Seq ID No: 282) | 1k | C |
| Myostatin- 2XTN8-18 kc | PDWCIDPDWWCKFWG SGSATGGSGSTASSGSG SATGPDWCIDPDWWC KFW | CCGGATTGGTGTATCGACCCGGACTG GTGGTGCAAATCTGGGGTTCTGGTTCC CGCTACCGGTGGTTCCGGTTCCACTG CTTCTTCTGGTTCCGGTTCTGCAACTG GTCCGGACTGGTGCATCGACCCGGAT TGGTGGTGTAATTTTGG (Seq ID No: 283) | 1k | C |
| Myostatin- 2XTN8-11 kc | ANWCVSPNWFCMVM GSGSATGGSGSTASSGSG GSATGANWCVSPNWF CMVM | CCGGATTGGTGTATCGACCCGGACTG GTGGTGCAAATCTGGGGTTCTGGTTCC CGCTACCGGTGGTTCCGGTTCCACTG CTTCTTCTGGTTCCGGTTCTGCAACTG GTCCGGACTGGTGCATCGACCCGGAT TGGTGGTGTAATTTTGG (Seq ID No; 284) | 1k | C |
| Myostatin- 2XTN8-25 kc | PDWCIDPDWWCKFWG SGSATGGSGSTASSGSG SATGPDWCIDPDWWC KFW | ACCACTGGTGCATCTCTCCGATGTG GTTCTGCTCTCAGCAGGGTTCTGGTTC CACTGCTTCTTCTGGTTCCGGTTCTGC AACTGGTACTACTTGGTGTATCTCTCC AATGTGGTTTTGTTCTCAGCAA (Seq ID No: 285) | 1k | C |
| Myostatin- 2XTN8-23 kc | HWACGYWPWSCKWV GSGSATGGSGSTASSGSG GSATGHWACGYWPWS CKWV | CACTGGGCATGTGGCTATTGGCCGTG GTCCTGCAAATGGGTTGGTTCTGGTTC CGCTACCGGTGGTTCCGGTTCCACTG CTTCTTCTGGTTCCGGTTCTGCAACTG GTCAGTGGGCTTGCGGTTACTGGCCG TGGTCTTGTAATGGGTT (Seq ID No: 286) | 1k | C |
| Myostatin-TN8- 29-19 kc | KKHCQIWTWMCAPKG SGSATGGSGSTASSGSG SATGQGHCTRWPWMC PPY | AAAAAACAAGTGTGAGATCTGGACTTG GATGTGCGCTCCGAAAGGTTCTGGTT CCGCTACCGGTGGTTCTGGTTCCACTG CTTCTTCTGGTTCCGGTTCCGCTACTG GTCAGGGTCACTGCACTCGTTGGCCA TGGATGTGTCCGCCGTAT (Seq ID No: 287) | 1k | C |
| Myostatin-TN8- 19-29 kc | QGHCTRWPWMCPPYG SGSATGGSGSTASSGSG SATGKKHCQIWTWMC | CAGGGTCACTGCACCCGTTGGCCGTG GATGTGCCCCCGGTACGGTTCTGGTT CCGCTACCGGTGGTTCTGGTTCCACTG | 1k | C |

| | | | | |
|-----------------------------|--|---|-------|---|
| | APK | CTTCTTCTGGTTCCGGTTCTGCTACTG GTAAAAAACAAGTCCAGATCTGGACT TGGATGTGCGCTCCGAAA (Seq ID No: 288) | | |
| Myostatin-TN8- 29-19 kn | KKHCQIWTWMCAPKG SGSATGGSGSTASSGSG SATGQGHCTRWPWMC PPY | AAAAAACAAGTCCAGATCTGGACTTG GATGTGCGCTCCGAAAGGTTCTGGTT CCGCTACCGGTGGTTCTGGTTCCACTG CTTCTTCTGGTTCCGGTTCCGCTACTG GTCAGGGTCACTGCACTCGTTGGCCA TGGATGTGTCGCGCTAT (Seq ID No: 289) | 1k | N |
| Myostatin-TN8- 29-19-8g | KKHCQIWTWMCAPKG GGGGGGGQGHCTRWP WMCPPY | AAAAAACAAGTCCAGATCTGGACTTG GATGTGCGCTCCGAAAGGTTGGTGGTG GTGGTGGCGGTGGCCAGGGTCACTGC ACCCGTTGGCCGTGGATGTGTCCGCC GTAT (Seq ID No: 290) | 8 gly | C |
| Myostatin-TN8- 19-29-6gc | QGHCTRWPWMCPPYG GGGGGKKHCQIWTW CAPK | CAGGGTCACTGCACCCGTGGCCGTG GATGTGCGCGCGTACGGTGGTGGTG GTGGTGGCAAAAAACAAGTCCAGATC TGGACTTGGATGTGCGCTCCGAAA (Seq ID No: 291) | 6 gly | C |

Example 3

In vitro Assays

5 C2C12 Cell Based Myostatin Activity Assay

This assay demonstrates the myostatin neutralizing capability of the inhibitor being tested by measuring the extent that binding of myostatin to its receptor is inhibited.

A myostatin-responsive reporter cell line was generated by transfection of C2C12 myoblast cells (ATCC No: CRL-1772) with a pMARE-luc construct. The pMARE-luc construct was made by cloning twelve repeats of the CAGA sequence, representing the myostatin/activin response elements (Dennler et al. EMBO 17: 3091-3100 (1998)) into a pLuc-MCS reporter vector (Stratagene cat # 219087) upstream of the TATA box. The myoblast C2C12 cells naturally express myostatin/activin receptors on its cell surface. When myostatin binds the cell receptors, the Smad pathway is activated, and phosphorylated Smad binds to the response element (Macias-Silva et al. Cell 87:1215 (1996)), resulting in the expression of the luciferase gene. Luciferase activity is then measured using a commercial luciferase reporter assay kit (cat # E4550, Promega, Madison, WI) according to manufacturer's protocol. A stable line of C2C12 cells that had been transfected with pMARE-luc (C2C12/pMARE clone #44) was used to measure myostatin activity according to the following procedure.

20 Equal numbers of the reporter cells (C2C12/pMARE clone #44) were plated into 96 well cultures. A first round screening using two dilutions of peptibodies was performed with the myostatin concentration fixed at 4 nM. Recombinant mature myostatin was pre-incubated for 2

hours at room temperature with peptibodies at 40 nM and 400 nM respectively. The reporter cell culture was treated with the myostatin with or without peptibodies for six hours. Myostatin activity was measured by determining the luciferase activity in the treated cultures. This assay was used to initially identify peptibody hits that inhibited the myostatin signaling activity in the reporter assay. Subsequently, a nine point titration curve was generated with the myostatin concentration fixed at 4 nM. The myostatin was preincubated with each of the following nine concentrations of peptibodies: 0.04 mM, 0.4 nM, 4 nM, 20 nM, 40 nM, 200 nM, 400 nM, 2 μ M and 4 μ M for two hours before adding the mixture to the reporter cell culture. The IC_{50} values were for a number of exemplary peptibodies are provided in Tables III and for affinity matured peptibodies, in Table VIII.

BIAcore® assay

An affinity analysis of each candidate myostatin peptibody was performed on a BIAcore®3000 (Biacore, Inc., Piscataway, NJ), apparatus using sensor chip CM5, and 0.005 percent P20 surfactant (Biacore, Inc.) as running buffer. Recombinant mature myostatin protein was immobilized to a research grade CM5 sensor chip (Biacore, Inc.) via primary amine groups using the Amine Coupling Kit (Biacore, Inc.) according to the manufacturer's suggested protocol.

Direct binding assays were used to screen and rank the peptibodies in order of their ability to bind to immobilized myostatin. Binding assays were carried by injection of two concentrations (40 and 400 nM) of each candidate myostatin-binding peptibody to the immobilized myostatin surface at a flow rate of 50 μ l/min for 3 minutes. After a dissociation time of 3 minutes, the surface was regenerated. Binding curves were compared qualitatively for binding signal intensity, as well as for dissociation rates. Peptibody binding kinetic parameters including k_a (association rate constant), k_d (dissociation rate constant) and K_D (dissociation equilibrium constant) were determined using the BIA evaluation 3.1 computer program (Biacore, Inc.). The lower the dissociation equilibrium constants (expressed in nM), the greater the affinity of the peptibody for myostatin. Examples of peptibody K_D values are shown in Table III and Table VI for affinity-matured peptibodies below.

Blocking assay on ActRIIB/Fc surface

Blocking assays were carried out using immobilized ActRIIB/Fc (R&D Systems, Minneapolis, MN) and myostatin in the presence and absence of peptibodies with the BIAcore® assay system. Assays were used to classify peptibodies as non-neutralizing (those which did not prevent myostatin binding to ActRIIB/Fc) or neutralizing (those that prevented myostatin binding

to ActRIIB/Fc). Baseline myostatin-ActRIIB/Fc binding was first determined in the absence of any peptibody.

For early screening studies, peptibodies were diluted to 4 nM, 40 nM, and 400 nM in sample buffer and incubated with 4 nM myostatin (also diluted in sample buffer). The peptibody: ligand mixtures were allowed to reach equilibrium at room temperature (at least 5 hours) and then were injected over the immobilized ActRIIB/Fc surface for 20 to 30 minutes at a flow rate of 10 μ L/min. An increased binding response (over control binding with no peptibody) indicated that peptibody binding to myostatin was non-neutralizing. A decreased binding response (compared to the control) indicated that peptibody binding to myostatin blocked the binding of myostatin to ActRIIB/Fc. Selected peptibodies were further characterized using the blocking assay of a full concentration series in order to derive IC_{50} values (for neutralizing peptibodies) or EC_{50} (for non-neutralizing peptibodies). The peptibody samples were serially diluted from 200 nM to 0.05 mM in sample buffer and incubated with 4 mM myostatin at room temperature to reach equilibrium (minimum of five hours) before injected over the immobilized ActRIIB/Fc surface for 20 to 30 minutes at a flow rate of 10 μ L/min. Following the sample injection, bound ligand was allowed to dissociate from the receptor for 3 minutes. Plotting the binding signal vrs. peptibody concentration, the IC_{50} values for each peptibody in the presence of 4 nM myostatin were calculated. It was found, for example, that the peptibodies TN8-19, L2 and L17 inhibit myostatin activity in cell-based assay, but binding of TN-8-19 does not block myostatin/ActRIIB/Fc interactions, indicating that TN-8-19 binds to a different epitope than that observed for the other two peptibodies.

Epitope binning for peptibodies

A purified peptibody was immobilized on a BIAcore chip to capture myostatin before injection of a second peptibody, and the amount of secondary peptibody bound to the captured myostatin was determined. Only peptibodies with distinct epitopes will bind to the captured myostatin, thus enabling the binning of peptibodies with similar or distinct epitope binding properties. For example, it was shown that peptibodies TN8-19 and L23 bind to different epitopes on myostatin.

Selectivity Assays

These assays were performed using BIAcore[®] technology, to determine the selectivity of binding of the peptibodies to other TGF β family members. ActRIIB/Fc, TGF β RII/Fc and BMPRII/Fc (all obtained from R & D Systems, Minneapolis, MN) were covalently coupled to research grade sensor chips according to manufacturer's suggested protocol. Because BIAcore assays

detects changes in the refractive index, the difference between the response detected with injection over the immobilized receptor surfaces compared with the response detected with injection over the control surface in the absence of any peptibody represents the actual binding of Activin A, TGF β 1, TGF β 3, and BMP4 to the receptors, respectively. With pre-incubation of peptibodies and TGF β molecules, a change (increase or decrease) in binding response indicates peptibody binding to the TGF β family of molecules. The peptibodies of the present invention all bind to myostatin but not to Activin A, TGF β 1, TGF β 3, or BMP4.

KinEx A™ Equilibrium Assays

Solution-based equilibrium-binding assays using KinExA™ technology (Sapidyne Instruments, Inc.) were used to determine the dissociation equilibrium (K_D) of myostatin binding to peptibody molecules. This solution-based assay is considered to be more sensitive than the BIAcore assay in some instances. Reacti-Gel™ 6X was pre-coated with about 50 ug/ml myostatin for over-night, and then blocked with BSA. 30pM and 100pM of peptibody samples were incubated with various concentrations (0.5 pM to 5 nM) of myostatin in sample buffer at room temperature for 8 hours before being run through the myostatin-coated beads. The amount of the bead-bound peptibody was quantified by fluorescent (Cy5) labeled goat anti-human-Fc antibody at 1 mg/ml in superblock. The binding signal is proportional to the concentration of free peptibody at equilibrium with a given myostatin concentration. K_D was obtained from the nonlinear regression of the competition curves using a dual-curve one-site homogeneous binding model provided in the KinEx A™ software (Sapidyne Instruments, Inc.).

Example 4

Comparison of Myostatin Inhibitors

The ability of three exemplary first-round peptibodies to bind to (K_D) and inhibit (IC_{50}) were compared with the K_D and IC_{50} values obtained for the soluble receptor fusion protein actRIIB/Fc (R & D Systems, Inc., Minneapolis, Minn.). The IC_{50} values were determined using the pMARE luc cell-based assay described in Example 3 and the K_D values were determined using the Biacore® assay described in Example 3.

TABLE III

| Inhibitor | IC_{50} (nM) | K_D (nM) |
|-------------|----------------|------------|
| ActRIIB/Fc | ~83 | ~7 |
| 2xTN8-19-kc | ~9 | ~2 |
| TN8-19 | ~23 | ~2 |

| | | |
|-----------|-----|-------|
| TN8-29 | ~26 | ~60 |
| TN12-34 | ~30 | ----- |
| Linear-20 | ~11 | ----- |

The peptibodies have an IC_{50} that is improved over the receptor/Fc inhibitor and binding affinities which are comparable in two peptibodies with the receptor/Fc.

5

Example 5

Comparison of Ability of Peptide and Peptibody to Inhibit Myostatin

The following peptide sequence: QGHCTRWPWMCPY (TN8-19) (SEQ ID NO: 33) was used to construct the corresponding peptibody TN8-19(pb) according to the procedure described in Example 2 above. Both the peptide alone and the peptibody were screened for myostatin inhibiting activity using the C2C12 based assay described in Example 3 above. It can be seen from Figure 1 the IC_{50} (effective concentration for fifty percent inhibition of myostatin) for the peptibody is significantly less than that of the peptide, and thus the ability of the peptide to inhibit myostatin activity has been substantially improved by placing it in the peptibody configuration.

15

Example 6

Generation of Affinity-Matured Peptides and Peptibodies

Several of the first round peptides used for peptibody generation were chosen for affinity maturation. The selected peptides included the following: the cysteine constrained TN8-19, QGHCTRWPWMCPY (SEQ ID NO: 33), and the linear peptides Linear-2
 20 MEMLDLSELLKDMVPISKA (SEQ ID NO: 104); Linear-15
 HHGWNLYLRKGSAPQWFEAWV (SEQ. ID NO: 117); Linear-17
 RATLLKDFWQLVEGYGDN (SEQ ID NO: 119); Linear-20 YREMSMLEGLLDVLERLQHY
 (SEQ ID NO: 122), Linear-21 HNSSQMLLSEIMLVGSMQ (SEQ ID NO: 123), Linear-24
 EFFHWLHNHRSEVNHWLDNMN (SEQ ID NO: 126). Based on a consensus sequence, directed
 25 secondary phage display libraries were generated in which the "core" amino acids (determined from the consensus sequence) were either held constant or biased in frequency of occurrence. Alternatively, an individual peptide sequence could be used to generate a biased, directed phage display library. Panning of such libraries under more stringent conditions can yield peptides with enhanced binding to myostatin, selective binding to myostatin, or with some additional desired
 30 property.

Production of doped oligos for libraries

Oligonucleotides were synthesized in a DNA synthesizer which were 91% "doped" at the core sequences, that is, each solution was 91% of the represented base (A, G, C, or T), and 3% of each of the other 3 nucleotides. For the TN8-19 family, for example, a 91% doped oligo used for the construction of a secondary phage library was the following:

5 5'-CAC AGT GCA CAG GGT NNK NNK NNK caK ggK caK tgK acK cgK tgK
 ccK tgK atK tgK ccK ccK taK NNK NNK NNK CAT TCT CTC GAG ATC A-3' (SEQ ID
 NO: 634)

10 wherein "N" indicates that each of the four nucleotides A, T, C, and G were equally represented,
 K indicates that G and T were equally represented, and the lower case letter represents a mixture
 of 91% of the indicated base and 3% of each of the other bases. The family of oligonucleotides
 prepared in this manner were PCR amplified as described above, ligated into a phagemid vectors,
 for example, a modified pCES1 plasmid (Dyax), or any available phagemid vector according to
 the protocol described above. The secondary phage libraries generated were all 91% doped and
 had between 1 and 6.5×10^9 independent transformants. The libraries were panned as described
 above, but with the following conditions:

Round 1 Panning:

Input phage number: 10^{12} - 10^{13} cfu of phagemid
 20 Selection method: Nunc Immuno Tube selection
 Negative selection: 2 X with Nunc Immuno Tubes coated with 2% BSA at 10 min. each
 Panning coating: Coat with 1 μ g of Myostatin protein in 1 ml of 0.1M Sodium carbonate buffer
 (pH 9.6)
 Binding time: 3 hours
 25 Washing conditions: 6 X 2%-Milk-PBST; 6 X PBST; 2 X PBS
 Elution condition: 100 mM TEA elution

Round 2 Panning:

Input phage number: 10^{11} cfu of phagemid
 30 Selection method: Nunc Immuno Tube selection
 Negative selection: 2 X with Nunc Immuno Tubes coated with 2% BSA at 30 min. each
 Panning coating: Coat with 1 μ g of Myostatin protein in 1 ml of 0.1M Sodium carbonate buffer
 (pH 9.6)
 Binding time: 1 hour
 35 Washing conditions: 15 X 2%-Milk-PBST, 1 X 2%-Milk-PBST for 1 hr., 10 X 2%-BSA-PBST,
 1 X 2%-BSA-PBST for 1 hr., 10 X PBST and 3 X PBS
 Elution condition: 100 mM TEA elution

Round 3 Panning:

Input phage number: 10^{10} cfu of phagemid
 40 Selection method: Nunc Immuno Tube selection
 Negative selection: 6 X with Nunc Immuno Tubes coated with 2% BSA at 10 min. each
 Panning coating: Coat with 0.1 μ g of Myostatin protein in 1 ml of 0.1M Sodium carbonate buffer
 (pH 9.6)
 45 Binding time: 1 hour

Washing conditions: 15 X 2%-Milk-PBST, 1 X 2%-Milk-PBST for 1 hr., 10 X 2%-BSA-PBST,
1 X 2%-BSA-PBST for 1 hr., 10 X PBST and 3 X PBS

Elution condition: 100 mM TEA elution

5 Panning of the secondary libraries yielded peptides with enhanced binding to myostatin.

Individual selected clones were subjected phage ELISA, as described above, and sequenced.

The following affinity matured TN8-19 family of peptides are shown in Table IV below.

| Affinity- matured peptibody | TABLE IV SEQ ID NO: | Peptide sequence |
|--------------------------------|---------------------------|-----------------------|
| mTN8-19-1 | 305 | VALHGQCTRWPWMCPPQREG |
| mTN8-19-2 | 306 | YPEQGLCTRWPWMCPPQTLA |
| mTN8-19-3 | 307 | GLNQGHCTRWPWMCPPQDSN |
| mTN8-19-4 | 308 | MITQGQCTRWPWMCPPQPSG |
| mTN8-19-5 | 309 | AGAEHCTRWPWMCAPNDWI |
| mTN8-19-6 | 310 | GVNQGQCTRWRWMCPNGWE |
| mTN8-19-7 | 311 | LADHGQCIRWPWMCPPEGWE |
| mTN8-19-8 | 312 | ILEQAQCTRWPWMCPPQRGG |
| mTN8-19-9 | 313 | TQTHAQCTRWPWMCPPQWEG |
| mTN8-19-10 | 314 | VVTQGHCTLWPWMCPPQRWR |
| mTN8-19-11 | 315 | IYPHDQCTRWPWMCPPQPYP |
| mTN8-19-12 | 316 | SYWQGQCTRWPWMCPPQWRG |
| mTN8-19-13 | 317 | MWQQGHCTRWPWMCPPQGWG |
| mTN8-19-14 | 318 | EFTQWHCTRWPWMCPPQRSQ |
| mTN8-19-15 | 319 | LDDQWQCTRWPWMCPPQGFS |
| mTN8-19-16 | 320 | YQTQGLCTRWPWMCPPQSQR |
| mTN8-19-17 | 321 | ESNQGQCTRWPWMCPPQGGW |
| mTN8-19-18 | 322 | WTDRGPCCTRWPWMCPPQANG |
| mTN8-19-19 | 323 | VGTTQGQCTRWPWMCPPYETG |
| mTN8-19-20 | 324 | PYEQGKCTRWPWMCPPYEVE |
| mTN8-19-21 | 325 | SEYQGLCTRWPWMCPPQGWK |
| mTN8-19-22 | 326 | TFSQGHCTRWPWMCPPQGWG |
| mTN8-19-23 | 327 | PGAHDHCTRWPWMCPPQSRY |
| mTN8-19-24 | 328 | VAEEWHCRRWPWMCPPQDWR |
| mTN8-19-25 | 329 | VGTTQGHCTRWPWMCPPQPAG |
| mTN8-19-26 | 330 | EEDQAHCRRWPWMCPPQGWV |
| mTN8-19-27 | 331 | ADTQGHCTRWPWMCPPQHWF |
| mTN8-19-28 | 332 | SGPQGHCTRWPWMCAPQGW |
| mTN8-19-29 | 333 | TLVQGHCTRWPWMCPPQRWV |
| mTN8-19-30 | 334 | GMAHGKCTRWAWMCPPQSWK |
| mTN8-19-31 | 335 | ELYHGQCTRWPWMCPPQSWA |
| mTN8-19-32 | 336 | VADHGHCTRWPWMCPPQGWG |
| mTN8-19-33 | 337 | PESQGHCTRWPWMCPPQGWG |
| mTN8-19-34 | 338 | IPAHGHCTRWPWMCPPQRWR |
| mTN8-19-35 | 339 | FTVHGHCTRWPWMCPPYGVV |
| mTN8-19-36 | 340 | PDFPGHCTRWRWMCPPQWE |
| mTN8-19-37 | 341 | QLWQGPCTQWPWMCPPKGRY |
| mTN8-19-38 | 342 | HANDGHCTRWQWMCPPQWGG |
| mTN8-19-39 | 343 | ETDHGLCTRWPWMCPPYGAR |
| mTN8-19-40 | 344 | GTWQGLCTRWPWMCPPQGWQ |
| mTN8-19 con1 | 345 | VATQGQCTRWPWMCPPQGWG |
| mTN8-19 con2 | 346 | VATQGQCTRWPWMCPPQRWG |

| | | |
|-------------|-----|----------------------|
| mTN8 con6-1 | 347 | QREWYPCYGGHLWCYDLHKA |
| mTN8 con6-2 | 348 | ISAWYSCYAGHFWCWDLKQK |
| mTN8 con6-3 | 349 | WTGWYQCYGGHLWCYDLRRK |
| mTN8 con6-4 | 350 | KTFWYPCYDGHFWCYNLKSS |
| mTN8 con6-5 | 351 | ESRWYPCYEGHLWCFDLTET |

The consensus sequence derived from the affinity- matured TN-8-19- 1 through Con2 (excluding the mTN8 con6 sequences) shown above is: C_{a1}a₂Wa₃WMCPP (SEQ ID NO: 352). All of these peptide comprise the sequence WMCPP (SEQ ID NO: 633). The underlined amino acids represent the core amino acids present in all embodiments, and a₁, a₂ and a₃ are selected from a neutral hydrophobic, neutral polar, or basic amino acid. In one embodiment of this consensus sequence, C_{b1}b₂Wb₃WMCPP (SEQ ID NO: 353), b₁ is selected from any one of the amino acids T, I, or R; b₂ is selected from any one of R, S, Q; and b₃ is selected from any one of P, R and Q. All of the peptides comprise the sequence WMCPP (SEQ ID NO: 633). A more detailed analysis of the affinity matured TN8 sequences comprising SEQ ID NO: 352 provides the following formula:

c₁c₂c₃c₄c₅c₆Cc₇c₈Wc₉WMCPPc₁₀c₁₁c₁₂c₁₃ (SEQ ID NO: 354), wherein:

c₁ is absent or any amino acid;

c₂ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

c₃ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

c₄ is absent or any amino acid;

c₅ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

c₆ is absent or a neutral hydrophobic, neutral polar, or basic amino acid;

c₇ is a neutral hydrophobic, neutral polar, or basic amino acid;

c₈ is a neutral hydrophobic, neutral polar, or basic amino acid;

c₉ is a neutral hydrophobic, neutral polar or basic amino acid; and wherein

c₁₀ to c₁₃ is any amino acid.

In one embodiment of the above formulation, b₇ is selected from any one of the amino acids T, I, or R; b₈ is selected from any one of R, S, Q; and b₉ is selected from any one of P, R and Q. This provides the following sequence:

d₁d₂d₃d₄d₅d₆Cd₇d₈Wd₉WMCPPd₁₀d₁₁d₁₂d₁₃ (SEQ ID NO: 355).

d₁ is absent or any amino acid;

d₂ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

d₃ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

d₄ is absent or any amino acid;

d₅ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

d₆ is absent or a neutral hydrophobic, neutral polar, or basic amino acid;

d₇ is selected from any one of the amino acids T, I, or R;

d₈ is selected from any one of R, S, Q;

d₉ is selected from any one of P, R and Q

and d₁₀ through d₁₃ are selected from any amino acid.

The consensus sequence of the mTN8 con6 series is WYe₁e₂Ye₃G, (SEQ ID NO: 356) wherein e₁ is P, S or Y; e₂ is C or Q, and e₃ is G or H.

5

In addition to the TN-19 affinity matured family, additional affinity matured peptides were produced from the linear L-2, L-15, L-17, L-20, L-21, and L-24 first round peptides. These families are presented in Table V below.

| Affinity matured peptibody | TABLE V | |
|----------------------------|------------|------------------------|
| | SEQ ID NO: | Peptide Sequence |
| L2 | 104 | MEMLDSLFELLKDMVPISKA |
| mL2-Con1 | 357 | RMEMLESLELLKEIVPMSKAG |
| mL2-Con2 | 358 | RMEMLESLELLKEIVPMSKAR |
| mL2-1 | 359 | RMEMLESLELLKDIVPMSKPS |
| mL2-2 | 360 | GMEMLESLELLQEIVPMSKAP |
| mL2-3 | 361 | RMEMLESLELLKDIVPISNPP |
| mL2-4 | 362 | RIEMLESLELLQEIVPISKA |
| mL2-5 | 363 | RMEMLQSLLELLKDIVPMSNAR |
| mL2-6 | 364 | RMEMLESLELLKEIVPTSNGT |
| mL2-7 | 365 | RMEMLESLELLKEIVPMSKAG |
| mL2-8 | 366 | RMEMLGSLELLKEIVPMSKAR |
| mL2-9 | 367 | QMELDSLELLKEIVPKSQPA |
| mL2-10 | 368 | RMEMLDSLELLKEIVPMSNAR |
| mL2-11 | 369 | RMEMLESLELLHEIVPMSQAG |
| mL2-12 | 370 | QMEMLESLLQLLKEIVPMSKAS |
| mL2-13 | 371 | RMEMLDSLELLKDMVPMITTGA |
| mL2-14 | 372 | RIEMLESLELLKDMVPMANAS |
| mL2-15 | 373 | RMEMLESLLQLLNEIVPMSRAR |
| mL2-16 | 374 | RMEMLESLELLKELVPMSKGV |
| mL2-17 | 375 | RIEMLESLELLKDIVPIQKAR |
| mL2-18 | 376 | RMELLESLELLKDMVPMSDSS |
| mL2-19 | 377 | RMEMLESLEVLQEIVPRAKGA |
| mL2-20 | 378 | RMEMLDSLLQLLNEIVPMSHAR |
| mL2-21 | 379 | RMEMLESLELLKDIVPMSNAG |
| mL2-22 | 380 | RMEMLQSLFELLKGMVPISKAG |
| mL2-23 | 381 | RMEMLESLELLKEIVPNSTAA |
| mL2-24 | 382 | RMEMLQSLLELLKEIVPISKAG |
| mL2-25 | 383 | RIEMLDSLELLNELVPMSKAR |
| L-15 | 117 | HHGWNYLRKGSAPQWF EAWV |
| mL15-con1 | 384 | QVESLQQLLMWLDQKLASGPQG |
| mL15-1 | 385 | RMELLESLELLKEMVPRSKAV |
| mL15-2 | 386 | QAVSLQHLLMWLDQKLASGPQH |

| | | |
|-----------|-----|-------------------------|
| mL15-3 | 387 | DEDSLQQLMWLDQKLASGPQL |
| mL15-4 | 388 | PVASLQQLIWLDQKLAQGPHA |
| mL15-5 | 389 | EVDELQQLLNWLDHKLASGPLQ |
| mL15-6 | 390 | DVESLEQLLMWLDHQLASGPHG |
| mL15-7 | 391 | QVDSLQQVLLWLEHKLALGPQV |
| mL15-8 | 392 | GDESLQHLLMWLEQKLALGPHG |
| mL15-9 | 393 | QIEMLESLLDLLRDMVPMSNAF |
| mL15-10 | 394 | EVDSLQQLMWLDQKLASGPQA |
| mL15-11 | 395 | EDESLQQLLIYLDKMLSSGPQV |
| mL15-12 | 396 | AMDQLHQLLIWLDHKLASGPQA |
| mL15-13 | 397 | RIEMLESLELLDEIALIPKAW |
| mL15-14 | 398 | EVVSLQHLLMWLEHKLASGPDG |
| mL15-15 | 399 | GGESLQQLMWLDQQLASGPQR |
| mL15-16 | 400 | GVESLQQLLIFLDHMLVSGPHD |
| mL15-17 | 401 | NVESLEHLLMMWLERLLASGPYA |
| mL15-18 | 402 | QVDSLQQLIWLDHQLASGPKR |
| mL15-19 | 403 | EVESLQQLMWLEHKLAAQGPQG |
| mL15-20 | 404 | EVDSLQQLMWLDQKLASGPHA |
| mL15-21 | 405 | EVDSLQQLMWLDQQLASGPQK |
| mL15-22 | 406 | GVEQLPQLLMWLEQKLASGPQR |
| mL15-23 | 407 | GEDSLQQLMWLDQQLAAGPQV |
| mL15-24 | 408 | ADDSLQQLMWLDRLKLASGPHV |
| mL15-25 | 409 | PVDSLQQLIWLDQKLASGPQG |
| L-17 | 119 | RATLLKDFWQLVEGYGDN |
| mL17-con1 | 410 | DWRATLLKEFWQLVEGLGDNLV |
| mL17-con2 | 411 | QSRATLLKEFWQLVEGLGDKQA |
| mL17-1 | 412 | DGRATLLTEFWQLVQGLGQKEA |
| mL17-2 | 413 | LARATLLKEFWQLVEGLGEKV |
| mL17-3 | 414 | GSRDTLLKEFWQLVVGLGDMQT |
| mL17-4 | 415 | DARATLLKEFWQLVDAYGDRMV |
| mL17-5 | 416 | NDRAQLLRDFWQLVDGLGVKSW |
| mL17-6 | 417 | GVRETLLEYLWYLLKGLGANQG |
| mL17-7 | 418 | QARATLLKEFCQLVGCQGDKLS |
| mL17-8 | 419 | QERATLLKEFWQLVAGLGQNMR |
| mL17-9 | 420 | SGRATLLKEFWQLVQGLGEYRW |
| mL17-10 | 421 | TM RATLLKEFWLVFDGQREMOW |
| mL17-11 | 422 | GERATLLNDFWQLVDGQGDNTG |
| mL17-12 | 423 | DERETLLKEFWQLVHGWGDNVA |
| mL17-13 | 424 | GGRATLLKELWQLLEGQGANLV |
| mL17-14 | 425 | TARATLLNELVQLVKGYGDKLV |
| mL17-15 | 426 | GMRATLLQEFWQLVGGQGDNWM |
| mL17-16 | 427 | STRATLLNDLWQLMKGWAEDRG |
| mL17-17 | 428 | SERATLLKELWQLVGGWGDNFG |
| mL17-18 | 429 | VGRATLLKEFWQLVEGLVGQSR |
| mL17-19 | 430 | EIRATLLKEFWQLVDEWREQPN |

| | | |
|-----------|-----|-------------------------|
| mL17-20 | 431 | QLRATLLKEFLQLVHGLGETDS |
| mL17-21 | 432 | TQRATLLKEFWQLIEGLGGKHV |
| mL17-22 | 433 | HYRATLLKEFWQLVDGLREQGV |
| mL17-23 | 434 | QSRVTLLREFWQLVESYRPIVN |
| mL17-24 | 435 | LSRATLLNEFWQFVDGQRDKRM |
| mL17-25 | 436 | WDRATLLNDFWHLMEELSQKPG |
| mL17-26 | 437 | QERATLLKEFWRMVEGLGKNRG |
| mL17-27 | 438 | NERATLLREFWQLVGGYGVNQR |
| L-20 | 122 | YREMSMLEGLLDVLERLQHY |
| mL20-1 | 439 | HQRDMSMLWELLDVLDGLRQYS |
| mL20-2 | 440 | TQRDMSMLDGLLEVLDQLRQQR |
| mL20-3 | 441 | TSRDMSLLWELLEELDRLGHQR |
| mL20-4 | 442 | MQHDMSMLYGLVELLES LGHQI |
| mL20-5 | 443 | WNRDMRMLLESLFEVLDGLRQQV |
| mL20-6 | 444 | GYRDMSMLEGLLAVLDRLGPQL |
| mL20 con1 | 445 | TQRDMSMLEGLLEVLDRLGQQR |
| mL20 con2 | 446 | WYRDMSMLEGLLEVLDRLGQQR |
| L-21 | 123 | HNSSQMLLSELIMLVGSM MQ |
| mL21-1 | 447 | TQNSRQMLLSDFMMLVGSMIQG |
| mL21-2 | 448 | MQTSRHILLSEFMMLVGSIMHG |
| mL21-3 | 449 | HDNSRQMLLSDDLHLVGTMIQG |
| mL21-4 | 450 | MENS RQNLLRELIMLVGNMSHQ |
| mL21-5 | 451 | QDTSRHMLLREFMMLVGEMIQG |
| mL21 con1 | 452 | DQNSRQMLLSDLMLVGSMIQG |
| L-24 | 126 | EFFHWLHNHRSEVNHVLD MN |
| mL24-1 | 453 | NVFFQWVQKHGRV VYQWLDINV |
| mL24-2 | 454 | FDFLQWLQNRSEVEHVL VMDV |

The affinity matured peptides provided in Tables IV and V are then assembled into peptibodies as described above and assayed using the in vivo assays.

- 5 The affinity matured L2 peptides comprise a consensus sequence of f_1 EML f_2 SL f_3 f_4 LL, (SEQ ID NO: 455), wherein f_1 is M or I; f_2 is any amino acid; f_3 is L or F; and f_4 is E, Q or D.

- The affinity matured L15 peptide family comprise the sequence $Lg_1g_2LLg_3g_4L$, (SEQ ID NO: 456), wherein g_1 is Q, D or E, g_2 is S, Q, D or E, g_3 is any amino acid, and g_4 is L, W, F, or Y.
- 10 The affinity matured L17 family comprises the sequence: $h_1h_2h_3h_4h_5h_6h_7h_8h_9$ (SEQ ID NO: 457) wherein h_1 is R or D; h_2 is any amino acid; h_3 is A, T, S or Q; h_4 is L or M; h_5 is L or S; h_6 is any amino acid; h_7 is F or E; h_8 is W, F or C; and h_9 is L, F, M or K. Consensus sequences may also be determined for the mL20, mL21 and mL24 families of peptides shown above.

- Peptibodies were constructed from these affinity matured peptides as described above,
- 15 using a linker attached to the Fc domain of human IgG1, having SEQ ID NO: 296, at the N-

terminus (N configuration), at the C terminus (C configuration) of the Fc, or at both the N and C terminals (N,C configurations), as described in Example 2 above. The peptides named were attached to the C or N terminals via a 5 glycine (5G), 8 glycine or k linker sequence. In the 2X peptibody version the peptides were linked with linkers such as 5 gly, 8 gly or k. Affinity matured peptides and peptibodies are designated with a small "m" such as mTN8-19-22 for example. Peptibodies of the present invention further contain two splice sites where the peptides were spliced into the phagemid vectors. The position of these splice sites are AQ—peptide—LE. The peptibodies generally include these additional amino acids (although they are not included in the peptide sequences listed in the tables). In some peptibodies the LE amino acids were removed from the peptides sequences. These peptibodies are designated -LE.

Exemplary peptibodies, and exemplary polynucleotide sequences encoding them, are provided in Table VI below. This table includes examples of peptibody sequences (as opposed to peptide only), such as the 2x mTN8-19-7 (SEQ ID NO: 615) and the peptibody with the LE sequences deleted (SEQ ID NO: 617). By way of explanation, the linker sequences in the 2x versions refers to the linker between the tandem peptides. These peptibody sequences contain the Fc, linkers, AQ and LE sequences. The accompanying nucleotide sequence encodes the peptide sequence in addition to the AQ/LE linker sequences, if present, but does not encode the designated linker.

TABLE VI

| Peptibody Name | Peptide | Nucleotide Sequence (SEQ ID No) | Linker | Term-inus |
|----------------|---------------------------|--|--------|-----------|
| mL2-Con1 | RMEMLESLELL KEIVPMSKAG | CGTATGGAAATGCTTGAATCTCTTC TTGAACTTCTTAAAGAAATTGTTCC AATGTCTAAAGCTGGT (SEQ ID NO: 458) | 5 gly | N |
| mL2-Con2 | RMEMLESLELL KEIVPMSKAR | CGTATGGAAATGCTTGAATCTCTTC TTGAACTTCTTAAAGAAATTGTTCC AATGTCTAAAGCTCGT (SEQ ID NO: 459) | 5 gly | N |
| mL2-1 | RMEMLESLELL KDIVPMSKPS | CGTATGGAAATGCTTGAATCTCTTC TTGAACTTCTTAAAGATATTGTTCC AATGTCTAAACCATCT (SEQ ID NO: 460) | 5 gly | N |
| mL2-2 | GMEMLESLELL QEIVPMSKAP | GGTATGGAAATGCTTGAATCTCTTT TTGAACTTCTTCAAGAAATTGTTCC AATGTCTAAAGCTCCA (SEQ ID NO: 461) | 5 gly | N |
| mL2-3 | RMEMLESLELL KDIVPISNPP | CGTATGGAAATGCTTGAATCTCTTC TTGAACTTCTTAAAGATATTGTTCC AATTTCTAATCCACCA (SEQ ID NO: 462) | 5 gly | N |

| | | | | |
|--------|----------------------------|--|-------|---|
| mL2-4 | RIEMLESLELLQ EIVPISKAE | CGTATTGAAATGCTTGAATCTCTTC TTGAACTTCTTCAAGAAATTGTTCC AATTTCTAAAGCTGAA (SEQ ID NO: 463) | 5 gly | N |
| mL2-5 | RMEMLQSLLELL KDIVPMSNAR | CGTATGGAAATGCTTCAATCTCTTC TTGAACTTCTTAAAGATATTGTTCC AATGTCTAATGCTCGT (SEQ ID NO: 464) | 5 gly | N |
| mL2-6 | RMEMLESLELL KEIVPTSNGT | CGTATGGAAATGCTTGAATCTCTTC TTGAACTTCTTAAAGAAATTGTTCC AACTTCTAATGGTACT (SEQ ID NO: 465) | 5 gly | N |
| mL2-7 | RMEMLESLELL KEIVPMSKAG | CGTATGGAAATGCTTGAATCTCTTT TTGAACTTCTTAAAGAAATTGTTCC AATGTCTAAAGCTGGT (SEQ ID NO: 466) | 5 gly | N |
| mL2-8 | RMEMLGSLELL KEIVPMSKAR | CGTATGGAAATGCTTGGTTCTCTTC TTGAACTTCTTAAAGAAATTGTTCC AATGTCTAAAGCTCGT (SEQ ID NO: 467) | 5 gly | N |
| mL2-9 | QMELLDSELELL KEIVPKSQPA | CAAATGGAACTTCTTGATTCTCTTT TTGAACTTCTTAAAGAAATTGTTCC AAAATCTCAACCAGCT (SEQ ID NO: 468) | 5 gly | N |
| mL2-10 | RMEMLDSLELL KEIVPMSNAR | CGTATGGAAATGCTTGATTCTCTTC TTGAACTTCTTAAAGAAATTGTTCC AATGTCTAATGCTCGT (SEQ ID NO: 469) | 5 gly | N |
| mL2-11 | RMEMLESLELL HEIVPMSQAG | CGTATGGAAATGCTTGAATCTCTTC TTGAACTTCTTCATGAAATTGTTCC AATGTCTCAAGCTGGT (SEQ ID NO: 470) | 5 gly | N |
| mL2-12 | QMEMLESLLQLL KEIVPMSKAS | CAAATGGAAATGCTTGAATCTCTTC TTCAACTTCTTAAAGAAATTGTTCC AATGTCTAAAGCTTCT (SEQ ID NO: 471) | 5 gly | N |
| mL2-13 | RMEMLDSLELL KDMVPMTTGA | CGTATGGAAATGCTTGATTCTCTTC TTGAACTTCTTAAAGATATGGTCC AATGACTACTGGTGCT (SEQ ID NO: 472) | 5 gly | N |
| mL2-14 | RIEMLESLELLK DMVPMANAS | CGTATTGAAATGCTTGAATCTCTTC TTGAACTTCTTAAAGATATGGTCC AATGGCTAATGCTTCT (SEQ ID NO: 473) | 5 gly | N |
| mL2-15 | RMEMLESLLQLL NEIVPMSRAR | CGTATGGAAATGCTTGAATCTCTTC TTCAACTTCTTAATGAAATTGTTCC AATGTCTCGTGCTCGT (SEQ ID NO: 474) | 5 gly | N |
| mL2-16 | RMEMLESLELL KELVPMSKGV | CGTATGGAAATGCTTGAATCTCTTT TTGATCTTCTTAAAGAACTTGTTC AATGTCTAAAGGTGTT (SEQ ID NO: 475) | 5 gly | N |
| mL2-17 | RIEMLESLELLK DIVPIQKAR | CGTATTGAAATGCTTGAATCTCTTC TTGAACTTCTTAAAGATATTGTTCC AATTCAAAAAGCTCGT (SEQ ID NO: 476) | 5 gly | N |

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| mL2-18 | RMELLESLELLK DMVPMSDSS | CGTATGGAACTTCTTGAATCTCTTT TTGAACTTCTTAAAGATATGGTTCC AATGTCTGATTCTTCT (SEQ ID NO: 477) | 5 gly | N |
| mL2-19 | RMEMLESLEVL QEIVPRAKGA | CGTATGGAAATGCTTGAATCTCTTC TTGAAGTTCTTCAAGAAATTGTTCC ACGTGCTAAAGGTGCT (SEQ ID NO: 478) | 5 gly | N |
| mL2-20 | RMEMLDSLLQLL NEIVPMSHAR | CGTATGGAAATGCTTGATTCTCTTC TTCAACTTCTTAATGAAATTGTTCC AATGTCTCATGCTCGT (SEQ ID NO: 479) | 5 gly | N |
| mL2-21 | RMEMLESLELL KDIVPMSNAG | CGTATGGAAATGCTTGAATCTCTTC TTGAACTTCTTAAAGATATTGTTCC AATGTCTAATGCTGGT (SEQ ID NO: 480) | 5 gly | N |
| mL2-22 | RMEMLQSLFELL KGMVPISKAG | CGTATGGAAATGCTTCAATCTCTTT TTGAACTTCTTAAAGGTATGGTTCC AATTTCTAAAGCTGGT (SEQ ID NO: 481) | 5 gly | N |
| mL2-23 | RMEMLESLELL KEIVPNSTAA | CGTATGGAAATGCTTGAATCTCTTC TTGAACTTCTTAAAGAAATTGTTCC AAATTCTACTGCTGCT (SEQ ID NO: 482) | 5 gly | N |
| mL2-24 | RMEMLQSLLELL KEIVPISKAG | CGTATGGAAATGCTTCAATCTCTTC TTGAACTTCTTAAAGAAATTGTTCC AATTTCTAAAGCTGGT (SEQ ID NO: 483) | 5 gly | N |
| mL2-25 | RIEMLDSLELLN ELVPMSKAR | CGTATTGAAATGCTTGATTCTCTTC TTGAACTTCTTAATGAACTTGTTCC AATGTCTAAAGCTCGT (SEQ ID NO: 484) | 5 gly | N |
| mL17-Con1 | DWRATLLKEFW QLVEGLGDNLV | GATTGGCGTGCTACTCTTCTTAAAG AATTTTGGCAACTTGTTGAAGGTCT TGGTGATAATCTTGTT (SEQ ID NO: 485) | 5 gly | N |
| mL17-1 | DGRATLLTEFWQ LVQGLGQKEA | GATGGTCGTGCTACTCTTCTTACTG AATTTTGGCAACTTGTTCAAGGTCT TGGTCAAAAAGAAGCT (SEQ ID NO: 486) | 5 gly | N |
| mL17-2 | LARATLLKEFWQ LVEGLGEKVV | CTTGCTCGTGCTACTCTTCTTAAAG AATTTTGGCAACTTGTTGAAGGTCT TGGTGAAAAAGTTGTT (SEQ ID NO: 487) | 5 gly | N |
| mL17-3 | GSRDTLLKEFWQ LVVGLGDMQT | GGTTCTCGTGATACTCTTCTTAAAG AATTTTGGCAACTTGTTGTTGGTCT TGGTGATATGCAAACT (SEQ ID NO: 488) | 5 gly | N |
| mL17-4 | DARATLLKEFWQ LVDAYGDRMV | GATGCTCGTGCTACTCTTCTTAAAG AATTTTGGCAACTTGTTGATGCTTA TGGTGATCGTATGGTT (SEQ ID NO: 489) | 5 gly | N |
| mL17-5 | NDRAQLLRDFWQ LVDGLGVKSW | AATGATCGTGCTCAACTTCTTCGTG ATTTTGGCAACTTGTTGATGGTCT TGGTGTTAAATCTTGG (SEQ ID NO: 490) | 5 gly | N |

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| mL17-6 | GVRETLLYELWY LLKGLGANQG | GGTGTTCGTGAAACTCTTCTTTATG AACTTTGGTATCTTCTTAAAGGTCT TGGTGCTAATCAAGGT (SEQ ID NO: 491) | 5 gly | N |
| mL17-7 | QARATLLKEFCQ LVGCQGDKLS | CAAGCTCGTGCTACTCTTCTTAAAG AATTTTGTCAACTTGTGGTTGTCA AGGTGATAAACTTTCT (SEQ ID NO: 492) | 5 gly | N |
| mL17-8 | QERATLLKEFWQ LVAGLGQNMR | CAAGAACGTGCTACTCTTCTTAAA GAATTTTGGCAACTTGTGCTGGTC TTGGTCAAAATATGCGT (SEQ ID NO: 493) | 5 gly | N |
| mL17-9 | SGRATLLKEFWQ LVQGLGEYRW | TCTGGTCGTGCTACTCTTCTTAAAG AATTTTGGCAACTTGTTCAGGTCT TGGTGAATATCGTTGG (SEQ ID NO: 494) | 5 gly | N |
| mL17-10 | TMRATLLKEFWL FVDGQREMQR | ACTATGCGTGCTACTCTTCTTAAAG AATTTTGGCTTTTGTGATGGTCA ACGTGAAATGCAATGG (SEQ ID NO: 495) | 5 gly | N |
| mL17-11 | GERATLLNDFWQ LVDGQGDNTG | GGTGAACGTGCTACTCTTCTTAATG ATTTTGGCAACTTGTGATGGTCA AGGTGATAATACTGGT (SEQ ID NO: 496) | 5 gly | N |
| mL17-12 | DERETLLKEFWQ LVHGWGDNVA | GATGAACGTGAAACTCTTCTTAAA GAATTTTGGCAACTTGTTCATGGTT GGGGTGATAATGTTGCT (SEQ ID NO: 497) | 5 gly | N |
| mL17-13 | GGRATLLKELWQ LLEGQGANLV | GGTGGTCGTGCTACTCTTCTTAAAG AACTTTGGCAACTCTTGAAGGTCA AGGTGCTAATCTTGT (SEQ ID NO: 498) | 5 gly | N |
| mL17-14 | TARATLLNELVQ LVKGYGDKLV | ACTGCTCGTGCTACTCTTCTTAATG AACTTGTTCAACTTGTAAAGGTTA TGGTGATAAACTTGT (SEQ ID NO: 499) | 5 gly | N |
| mL17-15 | GMRATLLQEFWQ LVGGQGDNWM | GGTATGCGTGCTACTCTTCTTCAAG AATTTTGGCAACTTGTGGTGGTCA AGGTGATAATTGGATG (SEQ ID NO: 500) | 5 gly | N |
| mL17-16 | STRATLLNDLWQ LMKGWAEDRG | TCTACTCGTGCTACTCTTCTTAATG ATCTTTGGCAACTTATGAAAGGTG GGCTGAAGATCGTGGT (SEQ ID NO: 501) | 5 gly | N |
| mL17-17 | SERATLLKELWQ LVGGWGDNFG | TCTGAACGTGCTACTCTTCTTAAAG AACTTTGGCAACTTGTGGTGGTTG GGGTGATAATTTGGT (SEQ ID NO: 502) | 5 gly | N |
| mL17-18 | VGRATLLKEFWQ LVEGLVGQSR | GTTGGTCGTGCTACTCTTCTTAAAG AATTTTGGCAACTTGTGAAGGTCT TGTGGTCAATCTCGT (SEQ ID NO: 503) | 5 gly | N |

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| 2x mTN8-Con6-(N)-1K | M-GAQ-WYPCYEGHFWC YDL-GSGSATGSGST ASSGSGSATG-WYPCYEGHFWC YDL-LE-5G-FC (SEQ ID NO: 504) | TGGTATCCGTGTTATGAGGGTCACT TCTGGTGCTACGATCTGGGTTCTGG TTCCACTGCTTCTTCTGGTTCCGGT TCCGCTACTGGTTGGTACCCGTGCT ACGAAGGTCACCTTTTGGTGTTATGA TCTG (SEQ ID NO: 505) | 1K | N |
| 2x mTN8-Con6-(C)-1K | FC-5G-AQ-WYPCYEGHFWC YDL-GSGSATGSGST ASSGSGSATG-WYPCYEGHFWC YDL-LE (SEQ ID NO: 506) | TGGTATCCGTGTTATGAGGGTCACT TCTGGTGCTACGATCTGGGTTCTGG TTCCACTGCTTCTTCTGGTTCCGGT TCCGCTACTGGTTGGTACCCGTGCT ACGAAGGTCACCTTTTGGTGTTATGA TCTG (SEQ ID NO: 507) | 1K | C |
| 2x mTN8-Con7-(N)-1K | M-GAQ-IFGCKWWDVQC YQF-GSGSATGSGST ASSGSGSATG-IFGCKWWDVQC YQF-LE-5G-FC (SEQ ID NO: 508) | ATCTTTGGCTGTAAATGGTGGGAC GTTCACTGCTACCAGTTCGGTTCTG GTTCCACTGCTTCTTCTGGTTCCGG TTCCGCTACTGGTATCTTCGGTTGC AAGTGGTGGGATGTACAGTGTTAT CAGTTT (SEQ ID NO: 509) | 1K | N |
| 2x mTN8-Con7-(C)-1K | FC-5G-AQ-IFGCKWWDVQC YQF-GSGSATGSGST ASSGSGSATG-IFGCKWWDVQC YQF-LE (SEQ ID NO: 510) | ATCTTTGGCTGTAAATGGTGGGAC GTTCACTGCTACCAGTTCGGTTCTG GTTCCACTGCTTCTTCTGGTTCCGG TTCCGCTACTGGTATCTTCGGTTGC AAGTGGTGGGATGTACAGTGTTAT CAGTTT (SEQ ID NO: 511) | 1K | C |
| 2x mTN8-Con8-(N)-1K | M-GAQ-IFGCKWWDVDC YQF-GSGSATGSGST ASSGSGSATG-IFGCKWWDVDC YQF-LE-5G-FC (SEQ ID NO: 512) | ATCTTTGGCTGTAAAGTGGTGGGAC GTTGACTGCTACCAGTTCGGTTCTG GTTCCACTGCTTCTTCTGGTTCCGG TTCCGCTACTGGTATCTTCGGTTGC AAATGGTGGGACGTTGATTGTTAT CAGTTT (SEQ ID NO: 513) | 1K | N |
| 2x mTN8-Con8-(C)-1K | FC-5G-AQ-IFGCKWWDVDC YQF-GSGSATGSGST ASSGSGSATG-IFGCKWWDVDC YQF-LE (SEQ ID NO: 514) | ATCTTTGGCTGTAAAGTGGTGGGAC GTTGACTGCTACCAGTTCGGTTCTG GTTCCACTGCTTCTTCTGGTTCCGG TTCCGCTACTGGTATCTTCGGTTGC AAATGGTGGGACGTTGATTGTTAT CAGTTT (SEQ ID NO: 515) | 1K | C |
| ML15-Con1 | QVESLQQLMWL DQKLASGPQG | CAGGTTGAATCCCTGCAGCAGCTG CTGATGTGGCTGGACCAGAACTG GCTTCCGGTCCGCAGGGT (SEQ ID NO: 516) | 5 gly | C |
| ML15-1 | RMELLESFELLK EMVPRSKAV | CGTATGGAAGTGGTGGTGGTGGT TTCGAAGTGGTGGTGGTGGTGGT CCGCGTTCCAAAGCTGTT (SEQ ID NO: 517) | 5 gly | C |

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| mL15-2 | QAVSLQHLLMWL LDQKLASGPQH | CAGGCTGTTCCCTGCAGCACCTGC TGATGTGGCTGGACCAGAACTGG CTTCCGGTCCGCAGCAC (SEQ ID NO: 518) | 5 gly | C |
| mL15-3 | DEDSLQQLMWL DQKLASGPQL | GACGAAGACTCCCTGCAGCAGCTG CTGATGTGGCTGGACCAGAACTG GCTTCCGGTCCGCAGCTG (SEQ ID NO: 519) | 5 gly | C |
| mL15-4 | PVASLQQLLIWL DQKLAQGPHA | CCGGTTGCTTCCCTGCAGCAGCTGC TGATCTGGCTGGACCAGAACTGG CTCAGGGTCCGCACGCT (SEQ ID NO: 520) | 5 gly | C |
| mL15-5 | EVDELQQLLNWL DHKLASGPLQ | GAAGTTGACGAACTGCAGCAGCTG CTGAACTGGCTGGACCACAACTG GCTTCCGGTCCGCTGCAG (SEQ ID NO: 521) | 5 gly | C |
| mL15-6 | DVESLEQLLMWL DHQLASGPHG | GACGTTGAATCCCTGGAACAGCTG CTGATGTGGCTGGACCACAGCTG GCTTCCGGTCCGCACGGT (SEQ ID NO: 522) | 5 gly | C |
| mL15-7 | QVDSLQQVLLWL EHKLALGPQV | CAGGTTGACTCCCTGCAGCAGGTT CTGCTGTGGCTGGAACACAACTG GCTCTGGGTCCGCAGGTT (SEQ ID NO: 523) | 5 gly | C |
| mL15-8 | GDESLQHLLMWL EQKLALGPHG | GGTGACGAATCCCTGCAGCACCTG CTGATGTGGCTGGAACAGAACTG GCTCTGGGTCCGCACGGT (SEQ ID NO: 524) | 5 gly | C |
| mL15-9 | QIEMLESLLDLR DMVPMSNAF | CAGATCGAAATGCTGGAATCCCTG CTGGACCTGCTGCGTGACATGGTTC CGATGTCCAACGCTTTC (SEQ ID NO: 525) | 5 gly | C |
| mL15-10 | EVDSLQQLMWL DQKLASGPQA | GAAGTTGACTCCCTGCAGCAGCTG CTGATGTGGCTGGACCAGAACTG GCTTCCGGTCCGCAGGCT (SEQ ID NO: 526) | 5 gly | C |
| mL15-11 | EDESLQQLLIYLD KMLSSGPQV | GAAGACGAATCCCTGCAGCAGCTG CTGATCTACCTGGACAAAATGCTG TCCTCCGGTCCGCAGGTT (SEQ ID NO: 527) | 5 gly | C |
| mL15-12 | AMDQLHQLLIWL DHKLASGPQA | GCTATGGACCAGCTGCACCAGCTG CTGATCTGGCTGGACCACAACTG GCTTCCGGTCCGCAGGCT (SEQ ID NO: 528) | 5 gly | C |
| mL15-13 | RIEMLESLELLD EIALIPKAW | CGTATCGAAATGCTGGAATCCCTG CTGGAATGCTGGACGAAATCGCT CTGATCCCGAAAGCTTGG (SEQ ID NO: 529) | 5 gly | C |
| mL15-14 | EVVSLQHLLMWL EHKLASGPDG | GAAGTTGTTTCCCTGCAGCACCTGC TGATGTGGCTGGAACACAACTGG CTTCCGGTCCGGACGGT (SEQ ID NO: 530) | 5 gly | C |
| mL15-15 | GGESLQQLMWL DQQLASGPQR | GGTGGTGAATCCCTGCAGCAGCTG CTGATGTGGCTGGACCAGCAGCTG GCTTCCGGTCCGCAGCGT (SEQ ID NO: 531) | 5 gly | C |

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| mL15-16 | GVESLQQLLIFLD HMLVSGPHD | GGTGTGAATCCCTGCAGCAGCTG CTGATCTTCCTGGACCACATGCTGG TTCCGGTCCGCACGAC (SEQ ID NO: 532) | 5 gly | C |
| mL15-17 | NVESLEHLMMW LERLLASGPYA | AACGTTGAATCCCTGGAACACCTG ATGATGTGGCTGGAACGTCTGCTG GCTCCGGTCCGTACGCT (SEQ ID NO: 533) | 5 gly | C |
| mL15-18 | QVDSLQQLLIWL DHQLASGPKR | CAGGTTGACTCCCTGCAGCAGCTG CTGATCTGGCTGGACCACCAGCTG GCTTCCGGTCCGAAACGT (SEQ ID NO: 534) | 5 gly | C |
| mL15-19 | EVESLQQLLMWL EHKLAQGPQG | GAAGTTGAATCCCTGCAGCAGCTG CTGATGTGGCTGGAACACAACTG GCTCAGGGTCCGCAGGGT (SEQ ID NO: 535) | 5 gly | C |
| mL15-20 | EVDSLQQLLMWL DQKLASGPHA | GAAGTTGACTCCCTGCAGCAGCTG CTGATGTGGCTGGACCAGAACTG GCTTCCGGTCCGCACGCT (SEQ ID NO: 536) | 5 gly | C |
| mL15-21 | EVDSLQQLLMWL DQQLASGPQK | GAAGTTGACTCCCTGCAGCAGCTG CTGATGTGGCTGGACCAGCAGCTG GCTTCCGGTCCGCAGAAA (SEQ ID NO: 537) | 5 gly | C |
| mL15-22 | GVEQLPQLLMWL EQKLASGPQR | GGTGTGAACAGCTGCCGCAGCTG CTGATGTGGCTGGAACAGAACTG GCTTCCGGTCCGCAGCGT (SEQ ID NO: 538) | 5 gly | C |
| mL15-23 | GEDSLQQLLMWL DQQLAAGPQV | GGTGAAGACTCCCTGCAGCAGCTG CTGATGTGGCTGGACCAGCAGCTG GCTGCTGGTCCGCAGGTT (SEQ ID NO: 539) | 5 gly | C |
| mL15-24 | ADDSLQQLLMW LDRKLASGPHV | GCTGACGACTCCCTGCAGCAGCTG CTGATGTGGCTGGACCGTAACTG GCTTCCGGTCCGCACGTT (SEQ ID NO: 540) | 5 gly | C |
| mL15-25 | PVDSLQQLLIWL DQKLASGPQG | CCGGTTGACTCCCTGCAGCAGCTG CTGATCTGGCTGGACCAGAACTG GCTTCCGGTCCGCAGGGT (SEQ ID NO: 541) | 5 gly | C |
| mL17-Con2 | QSRATLLKEFWQ LVEGLGDKQA | CAGTCCCGTGCTACCCTGCTGAAA GAATTCTGGCAGCTGGTTGAAGGT CTGGGTGACAAACAGGCT (SEQ ID NO: 542) | 5 gly | C |
| mL17-19 | EIRATLLKEFWQL VDEWREQPN | GAAATCCGTGCTACCCTGCTGAAA GAATTCTGGCAGCTGGTTGACGAA TGGCGTGAACAGCCGAAC (SEQ ID NO: 543) | 5 gly | C |
| mL17-20 | QLRATLLKEFLQL VHGLGETDS | CAGCTGCGTGCTACCCTGCTGAAA GAATTCCTGCAGCTGGTTCACGGTC TGGGTGAAACCGACTCC (SEQ ID NO: 544) | 5 gly | C |
| mL17-21 | TQRATLLKEFWQ LIEGLGGKHV | ACCCAGCGTGCTACCCTGCTGAAA GAATTCCTGGCAGCTGATCGAAGGT CTGGGTGTTAAACACGTT (SEQ ID NO: 545) | 5 gly | C |

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| mL17-22 | HYRATLLKEFWQ LVDGLREQGV | CACTACCGTGCTACCCTGCTGAAA GAATTCTGGCAGCTGGTTGACGGT CTGCGTGAACAGGGTGTT (SEQ ID NO: 546) | 5 gly | C |
| mL17-23 | QSRVTLLREFWQ LVESYRPIVN | CAGTCCCGTGTTACCCTGCTGCGTG AATTCTGGCAGCTGGTTGAATCCTA CCGTCCGATCGTTAAC (SEQ ID NO: 547) | 5 gly | C |
| mL17-24 | LSRATLLNEFWQ FVDGQRDKRM | CTGTCCCGTGCTACCCTGCTGAACG AATTCTGGCAGTTCGTTGACGGTCA GCGTGACAAACGTATG (SEQ ID NO: 548) | 5 gly | C |
| mL17-25 | WDRATLLNDFW HLMEELSQKPG | TGGGACCGTGCTACCCTGCTGAAC GACTTCTGGCACCTGATGGAAGAA CTGTCCCGAGAAACCGGGT (SEQ ID NO: 549) | 5 gly | C |
| mL17-26 | QERATLLKEFWR MVEGLGKNRG | CAGGAACGTGCTACCCTGCTGAAA GAATTCTGGCGTATGGTTGAAGGT CTGGGTAAAAACCGTGGT (SEQ ID NO: 550) | 5 gly | C |
| mL17-27 | NERATLLREFWQ LVGGYGVNQR | AACGAACGTGCTACCCTGCTGCGT GAATTCTGGCAGCTGGTTGGTGGTT ACGGTGTTAACCAGCGT (SEQ ID NO: 551) | 5 gly | C |
| mTN8Con6-1 | QREWYPCYGGHL WCYDLHKA | CAGCGTGAATGGTACCGTGCTAC GGTGGTCACCTGTGGTGCTACGAC CTGCACAAAGCT (SEQ ID NO: 552) | 5 gly | C |
| mTN8Con6-2 | ISAWYSCYAGHF WCWDLKQK | ATCTCCGCTTGGTACTCCTGCTACG CTGGTCACCTCTGGTGCTGGGACCT GAAACAGAAA (SEQ ID NO: 553) | 5 gly | C |
| mTN8Con6-3 | WTGWYQCYGGH LWCYDLRRK | TGGACCGGTTGGTACCAGTGCTAC GGTGGTCACCTGTGGTGCTACGAC CTGCGTCGTAAA (SEQ ID NO: 554) | 5 gly | C |
| mTN8Con6-4 | KTFWYPCYDGHF WCYNLKSS | AAAACCTTCTGGTACCCGTGCTAC GACGGTCACCTCTGGTGCTACAAC CTGAAATCCTCC (SEQ ID NO: 545) | 5 gly | C |
| mTN8Con6-5 | ESRWYPCYEGHL WCFDLTET | GAATCCCGTTGGTACCCGTGCTAC GAAGTCACTGTGGTGCTTCGAC CTGACCGAAACC (SEQ ID NO: 546) | 5 gly | C |
| mL24-1 | NVFFQWVQKHG RVVYQWLDINV | AATGTTTTTTTTCAATGGGTTCAAA AACATGGTCGTGTTGTTATCAATG GCTTGATATTAATGTT (SEQ ID NO: 557) | 5 gly | C |
| mL24-2 | FDFLQWLQNHRS EVEHWLVMDV | TTTGATTTTCTTCAATGGCTTCAAA ATCATCGTTCTGAAGTTGAACATTG GCTTGTTATGGATGTT (SEQ ID NO: 558) | 5 gly | C |
| mL20-1 | HQRDMSMLWEL LDVLDGLRQYS | CATCAACGTGATATGTCTATGCTTT GGGAACCTTCTTGATGTTCTTGATGG TCTTCGTCAATATTCT (SEQ ID NO: 559) | 5 gly | C |
| mL20-2 | TQRDMSMLDGLL EVLDQLRQQR | ACTCAACGTGATATGTCTATGCTTG ATGGTCTTCTGAAGTTCTTGATCA ACTTCGTCAACAACGT (SEQ ID | 5 gly | C |

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| mL20-3 | TSRDMSLLWELL EELDRLGHQR | ACCTCCCGTGACATGTCCCTGCTGT GGGAACTGCTGGAAGAACTGGACC GTCTGGGTCACCAGCGT (SEQ ID NO: 561) | 5 gly | C |
| mL20-4 | MQHDMSMLYGL VELLESLGHI | ATGCAACATGATATGTCTATGCTTT ATGGTCTTGTTGAACTTCTTGAATC TCTTGGTCATCAAATT (SEQ ID NO: 562) | 5 gly | C |
| mL20-5 | WNRDMRMLES FEVLDGLRQV | TGGAATCGTGATATGCGTATGCTTG AATCTCTTTTGAAGTTCTTGATGG TCTTCGTCAACAAGTT (SEQ ID NO: 563) | 5 gly | C |
| mL20-6 | GYRDMSMLEGL AVLDRLGPQL | GGTATCGTGATATGTCTATGCTTG AAGGTCTTCTTGCTGTTCTTGATCG TCTTGGTCCACAATT (SEQ ID NO: 564) | 5 gly | C |
| mL20 Con1 | TQRDMSMLEGL EVLDRLGQR | ACTCAACGTGATATGTCTATGCTTG AAGGTCTTCTTGAAGTTCTTGATCG TCTTGGTCAACAACGT (SEQ ID NO: 565) | 5 gly | C |
| mL20 Con2 | WYRDMSMLEGL LEVLDRLGQR | TGGTACCGTGACATGTCCATGCTG GAAGGTCTGCTGGAAGTTCTGGAC CGTCTGGGTCAGCAGCGT (SEQ ID NO: 566) | 5 gly | C |
| mL21-1 | TQNSRQMLLSDF MMLVGSMIQG | ACTCAAAATTCTCGTCAAATGCTTC TTTCTGATTTTATGATGCTTGTTGG TTCTATGATTCAAGGT (SEQ ID NO: 567) | 5 gly | C |
| mL21-2 | MQTSRHILLSEFM MLVGSIMHG | ATGCAAACTTCTCGTCATATTCTTC TTTCTGAATTTATGATGCTTGTTGG TTCTATTATGCATGGT (SEQ ID NO: 568) | 5 gly | C |
| mL21-3 | HDNSRQMLLSDL LHLVGTMIQG | CACGACAACTCCCGTCAGATGCTG CTGTCGACCTGCTGCACCTGGTTG GTACCATGATCCAGGGT (SEQ ID NO: 569) | 5 gly | C |
| mL21-4 | MENSRQNLLRELI MLVGNMSHQ | ATGGAAAACTCCCGTCAGAACCTG CTGCGTGAAGTATCATGCTGGTTG GTAACATGTCCCACCAG (SEQ ID NO: 570) | 5 gly | C |
| mL21-5 | QDTSRHMLLREF MMLVGEMIQG | CAGGACACCTCCCGTCACATGCTG CTGCGTGAATTCATGATGCTGGTTG GTGAAATGATCCAGGGT (SEQ ID NO: 571) | 5 gly | C |
| mL21 Con1 | DQNSRQMLLSDL MMLVGSMIQG | GACCAGAACTCCCGTCAGATGCTG CTGTCGACCTGATGATCCTGGTTG GTCCATGATCCAGGGT (SEQ ID NO: 572) | 5 gly | C |
| mTN8-19-1 | VALHGQCTRWP WMCPQREG | GTTGCTCTTCATGGTCAATGTACTC GTTGGCCATGGATGTGTCCACCAC AACGTGAAGGT (SEQ ID NO: 573) | 5 gly | C |

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| mTN8-19-2 | YPEQGLCTRWPW MCPPQTLA | TATCCAGAACAAGGTCTTTGTACTC GTTGGCCATGGATGTGTCCACCAC AAACTCTTGCT (SEQ ID N: 574) | 5 gly | C |
| mTN8-19-3 | GLNQGHCTRWP WMCPPQDSN | GGTCTGAACCAGGGTCACTGCACC CGTTGGCCGTGGATGTGCCCCGCCG CAGGACTCCAAC (SEQ ID NO: 575) | 5 gly | C |
| mTN8-19-4 | MITQGQCTRWPW MCPPQPSG | ATGATTACTCAAGGTCAATGTACTC GTTGGCCATGGATGTGTCCACCAC AACCATCTGGT (SEQ ID NO: 576) | 5 gly | C |
| mTN8-19-5 | AGAEHCTRWP WMCAPNDWI | GCTGGTGCTCAGGAACACTGCACC CGTTGGCCGTGGATGTGCGCTCCG AACGACTGGATC (SEQ ID NO: 577) | 5 gly | C |
| mTN8-19-6 | GVNQGQCTRWR WMCPPNGWE | GGTGTTAACCAGGGTCAGTGCACC CGTTGGCGTTGGATGTGCCCCGCCG AACGGTTGGGAA (SEQ ID NO: 578) | 5 gly | C |
| mTN8-19-7 | LADHGQCIRWPW MCPPEGWE | CTGGCTGACCACGGTCAGTGCATC CGTTGGCCGTGGATGTGCCCCGCCG GAAGGTTGGGAA (SEQ ID NO: 579) | 5 gly | C |
| mTN8-19-8 | ILEQAQCTRWPW MCPPQRGG | ATCCTGGAACAGGTCAGTGCACC CGTTGGCCGTGGATGTGCCCCGCCG CAGCGTGGTGGT (SEQ ID NO: 580) | 5 gly | C |
| mTN8-19-9 | TQTHAQCTRWP WMCPPQWEG | ACTCAAACATGCTCAATGTACTC GTTGGCCATGGATGTGTCCACCAC AATGGGAAGGT (SEQ ID NO: 581) | 5 gly | C |
| mTN8-19-10 | VVTQGHCTLWP WMCPPQRWR | GTTGTTACTCAAGGTCATTGTACTC TTTGGCCATGGATGTGTCCACCACA ACGTTGGCGT (SEQ ID NO: 582) | 5 gly | C |
| mTN8-19-11 | IYPHDQCTRWPW MCPPQPYP | ATTTATCCACATGATCAATGTACTC GTTGGCCATGGATGTGTCCACCAC AACCATATCCA (SEQ ID NO: 583) | 5 gly | C |
| mTN8-19-12 | SYWQQQCTRWP WMCPPQWRG | TCTTATTGGCAAGGTCAATGTACTC GTTGGCCATGGATGTGTCCACCAC AATGGCGTGGT (SEQ ID NO: 584) | 5 gly | C |
| mTN8-19-13 | MWQQGHCTRWP WMCPPQGWG | ATGTGGCAACAAGGTCATTGTACTC CGTTGGCCATGGATGTGTCCACCA CAAGGTTGGGT (SEQ ID NO: 585) | 5 gly | C |
| mTN8-19-14 | EFTQWHCTRWP WMCPPQRSQ | GAATTCACCCAGTGGCACTGCACC CGTTGGCCGTGGATGTGCCCCGCCG CAGCGTCCAG (SEQ ID NO: 586) | 5 gly | C |
| mTN8-19-15 | LDDQWQCTRWP WMCPPQGFS | CTGGACGACCAAGTGGCAGTGCACC CGTTGGCCGTGGATGTGCCCCGCCG CAGGGTTTCTCC (SEQ ID NO: 587) | 5 gly | C |
| mTN8-19-16 | YQTQGLCTRWP WMCPPQSQR | TATCAAACATCAAGGTCTTTGTACTC GTTGGCCATGGATGTGTCCACCAC AATCTCAACGT (SEQ ID NO: 588) | 5 gly | C |
| mTN8-19-17 | ESNQGQCTRWP WMCPPQGGW | GAATCTAATCAAGGTCAATGTACTC CGTTGGCCATGGATGTGTCCACCA CAAGGTGGTTGG (SEQ ID NO: 589) | 5 gly | C |

| | | | | |
|------------|----------------------------|---|-------|---|
| mTN8-19-18 | WTD RGPCTRWP WMCPPQANG | TGGACCGACCGTGGTCCGTGCACC CGTTGGCCGTGGATGTGCCCCCGG CAGGCTAACGGT (SEQ ID NO: 590) | 5 gly | C |
| mTN8-19-19 | VGTQ GQCTRWP WMCPPYETG | GTTGGTACCCAGGGTCAGTGCACC CGTTGGCCGTGGATGTGCCCCCGG TACGAAACCGGT (SEQ ID NO: 591) | 5 gly | C |
| mTN8-19-20 | PYE QGKCTRWP WMCPPYEVE | CCGTACGAACAGGGTAAATGCACC CGTTGGCCGTGGATGTGCCCCCGG TACGAAGTTGAA (SEQ ID NO: 592) | 5 gly | C |
| mTN8-19-21 | SEYQ GLCTRWPW MCP PQGWK | TCCGAATACCAGGGTCTGTGCACC CGTTGGCCGTGGATGTGCCCCCGG CAGGGTTGAAA (SEQ ID NO: 593) | 5 gly | C |
| mTN8-19-22 | TFSQ GHCTRWPW MCP PQGWG | ACCTTCTCCCAGGGTCACTGCACCC GTTGGCCGTGGATGTGCCCCCGG AGGGTTGGGGT (SEQ ID NO: 594) | 5 gly | C |
| mTN8-19-23 | PGA HDHCTRWP WMCPPQSR Y | CCGGGTGCTCACGACCACTGCACC CGTTGGCCGTGGATGTGCCCCCGG CAGTCCCGTTAC (SEQ ID NO: 595) | 5 gly | C |
| mTN8-19-24 | VAEE WHCRRWP WMCPPQDWR | GTTGCTGAAGAATGGCACTGCCGT CGTTGGCCGTGGATGTGCCCCCGG CAGGACTGGCGT (SEQ ID NO: 596) | 5 gly | C |
| mTN8-19-25 | VGTQ GHCTRWP WMCPPQAG | GTTGGTACCCAGGGTCACTGCACC CGTTGGCCGTGGATGTGCCCCCGG CAGCCGGCTGGT (SEQ ID NO: 597) | 5 gly | C |
| mTN8-19-26 | EEDQA HCRSWP WMCPPQGWV | GAAGAAGACCAGGCTCACTGCCGT TCCTGGCCGTGGATGTGCCCCCGG CAGGGTTGGGTT (SEQ ID NO: 598) | 5 gly | C |
| mTN8-19-27 | ADTQ GHCTRWP WMCPPQHW F | GCTGACACCCAGGGTCACTGCACC CGTTGGCCGTGGATGTGCCCCCGG CAGCACTGGTTC (SEQ ID NO: 599) | 5 gly | C |
| mTN8-19-28 | SGPQ GHCTRWPW MCA PQGWF | TCCGGTCCGCAGGGTCACTGCACC CGTTGGCCGTGGATGTGCGCTCCG CAGGGTTGGTTC (SEQ ID NO: 600) | 5 gly | C |
| mTN8-19-29 | TLVQ GHCTRWP WMCPPQRWV | ACCCTGGTTCAGGGTCACTGCACC CGTTGGCCGTGGATGTGCCCCCGG CAGCGTTGGGTT (SEQ ID NO: 601) | 5 gly | C |
| mTN8-19-30 | GMAHG KCTRWA WMCPPQSWK | GGTATGGCTCACGGTAAATGCACC CGTTGGGCTTGGATGTGCCCCCGG CAGTCCTGGAAA (SEQ ID NO: 602) | 5 gly | C |
| mTN8-19-31 | ELYHG QCTRWP WMCPPQSWA | GAAGTGTACCACGGTCAGTGCACC CGTTGGCCGTGGATGTGCCCCCGG CAGTCCTGGGCT (SEQ ID NO: 603) | 5 gly | C |
| mTN8-19-32 | VADHG HCTRWP WMCPPQGWG | GTTGCTGACCACGGTCACTGCACC CGTTGGCCGTGGATGTGCCCCCGG CAGGGTTGGGGT (SEQ ID NO: 604) | 5 gly | C |
| mTN8-19-33 | PESQ GHCTRWPW MCP PQGWG | CCGGAATCCCAGGGTCACTGCACC CGTTGGCCGTGGATGTGCCCCCGG CAGGGTTGGGGT (SEQ ID NO: 605) | 5 gly | C |

| | | | | |
|-----------------------------------|--|--|-------|---|
| mTN8-19-34 | IPAHGHCTRWPW MCPPQRWR | ATCCCGGCTCACGGTCACTGCACC CGTTGGCCGTGGATGTGCCCCCG CAGCGTTGGCGT (SEQ ID NO: 606) | 5 gly | C |
| mTN8-19-35 | FTVHGHCTRWP WMCPPYGWV | TTCACCGTTCACGGTCACTGCACCC GTTGGCCGTGGATGTGCCCCCGT ACGGTTGGGTT (SEQ ID NO: 607) | 5 gly | C |
| mTN8-19-36 | PDFPGHCTRWRW MCPPQWE | CCAGATTTCCAGGTCATTGTACTC GTTGGCGTTGGATGTGTCCACCAC AAGGTTGGGAA (SEQ ID NO: 608) | 5 gly | C |
| mTN8-19-37 | QLWQGPCTQWP WMCPPKGRY | CAGCTGTGGCAGGGTCCGTGCACC CAGTGGCCGTGGATGTGCCCCCG AAAGGTCGTTAC (SEQ ID NO: 609) | 5 gly | C |
| mTN8-19-38 | HANDGHCTRWQ WMCPPQWGG | CACGCTAACGACGGTCACTGCACC CGTTGGCAGTGGATGTGCCCCCG CAGTGGGGTGGT (SEQ ID NO: 610) | 5 gly | C |
| mTN8-19-39 | ETDHGLCTRWPW MCPPYGAR | GAAACCGACCACGGTCTGTGCACC CGTTGGCCGTGGATGTGCCCCCG TACGGTGCTCGT (SEQ ID NO: 611) | 5 gly | C |
| mTN8-19-40 | GTWQGLCTRWP WMCPPQGWQ | GGTACCTGGCAGGGTCTGTGCACC CGTTGGCCGTGGATGTGCCCCCG CAGGTTGGCAG (SEQ ID NO: 612) | 5 gly | C |
| mTN8-19 Con1 | VATQGQCTRWP WMCPPQGWG | GTTGCTACCCAGGGTCAGTGCACC CGTTGGCCGTGGATGTGCCCCCG CAGGTTGGGGT (SEQ ID NO: 613) | 5 gly | C |
| mTN8-19 Con2 | VATQGQCTRWP WMCPPQRWG | GTTGCTACCCAGGGTCAGTGCACC CGTTGGCCGTGGATGTGCCCCCG CAGCGTTGGGGT (SEQ ID NO: 614) | 5 gly | C |
| 2X mTN8-19-7 | FC-5G-AQ- LADHGQCIRWPW MCPPEGWELEGS GSATGSGSTASS SGSATGLADHG QCIRWPWMCPPE GWE-LE (SEQ ID NO: 615) | CTTGCTGATCATGGTCAATGTATTC GTTGGCCATGGATGTGTCCACCAG AAGGTTGGGAACGAGGGTTCCG GTTCCGCTACCGCGGCTCTGGCTC CACTGCTTCTCCGGTTCCGGTTCT GCTACTGGTCTGGCTGACCACGGT CAGTGCATCCGTTGGCCGTGGATG TGCCCCCGGAAGGTTGGGAACTG GAA (SEQ ID NO: 616) | 1K | C |
| 2X mTN8-19-7 ST—GG del2x LE | FC-5G-AQ- LADHGQCIRWPW MCPPEGWEGSGS ATGSGGGASSG SGSATGLADHGQ CIRWPWMCPPEG WE (SEQ ID NO: 617) | CTTGCTGATCATGGTCAATGTATTC GTTGGCCATGGATGTGTCCACCAG AAGGTTGGGAAGGTTCCGGTTCCG CTACCGGCGGCTCTGGCGGTGGCG CTTCTTCCGGTTCCGGTTCTGCTAC TGGTCTGGCTGACCACGGTCAGTG CATCCGTTGGCCGTGGATGTGTCCA CCAGAAGGTTGGGAA (SEQ ID NO: 618) | 1K | C |

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|------------------------------------|---|--|----|---|
| 2X mTN8-19-21 | FC-5G-AQ- SEYQGLCTRWPW MCP PQWKLEGS GSATGSGSTASS SGSATGSEYQG LCTRWPWMCP PQ GWK -LE (SEQ ID NO: 619) | TCTGAATATCAAGGTCTTTGTACTC GTTGGCCATGGATGTGTCCACCAC AAGGTTGGAAACTCGAGGGTTCCG GTTCCGCTACCGGCGGCTCTGGCTC CACTGCTTCTTCCGGTCCGGTTCT GCTACTGGTTCTGAGTATCAAGGC CTCTGTACTCGCTGGCCATGGATGT GTCCACCACAAGGCTGGAAGCTGG AA (SEQ ID NO: 620) | 1K | C |
| 2X mTN8-19-21 ST—GG del2x LE | FC-5G-AQ- SEYQGLCTRWPW MCP PQWKSGS ATGSGGGASSG SGSATGSEYQGL CTRWPWMCP PQ GWK (SEQ ID NO: 621) | TCTGAATATCAAGGTCTTTGTACTC GTTGGCCATGGATGTGTCCACCAC AAGGTTGGAAAGGTTCCGGTTCCG CTACCGGCGGCTCTGGCGGTGGCG CTTCTTCCGGTCCGGTTCTGCTAC TGGTCTGAGTATCAAGGCCTCTGT ACTCGCTGGCCATGGATGTGTCCA CCACAAGGTTGGAAA (SEQ ID NO: 622) | 1K | C |
| 2X mTN8-19-22 | FC-5G-AQ- TFSQGHCTRWPW MCP PQWGLEGS GSATGSGSTASS SGSATGTFSQG HCTRWPWMCP P QGWG -L E (SEQ ID NO: 623) | ACTTTTCTCAAGGTCATTGTACTC GTTGGCCATGGATGTGTCCACCAC AAGGTTGGGGTCTCGAGGGTTCCG GTTCCGCTACCGGCGGCTCTGGCTC CACTGCTTCTTCCGGTCCGGTTCT GCTACTGGTACTTTTCTCAAGGCC ATTGTACTCGCTGGCCATGGATGTG TCCACCACAAGGCTGGGGCCTGGA A (SEQ ID NO: 624) | 1K | C |
| 2X mTN8-19-32 | FC-5G-AQ- VADHGHCTRWP WMCP PQWGLE GSATGSGSGST ASSGSGSATGVA DHGHCTRWPWM CPPQGWG-LE (SEQ ID NO: 625) | GTTGCTGATCATGGTCATTGTACTC GTTGGCCATGGATGTGTCCACCAC AAGGTTGGGGTCTCGAGGGTTCCG GTTCCGCAACCGGCGGCTCTGGCT CCACTGCTTCTTCCGGTCCGGTTC TGCTACTGGTGTGCTGACCACGGT CACTGCACCCGTTGGCCGTGGATG TGCCCGCCGACAGGTTGGGGTCTG GAA (SEQ ID NO: 626) | 1K | C |
| 2X mTN8-19-32 ST—GG del2x LE | FC-5G-AQ- VADHGHCTRWP WMCP PQWGGS GSATGSGGGAS SGSGSATGVADH GHCTRWPWVCP P QGWG (SEQ ID NO: 627) | GTTGCTGATCATGGTCATTGTACTC GTTGGCCATGGATGTGTCCACCAC AAGGTTGGGGTGGTTCCGGTTCCG CTACCGGCGGCTCTGGCGGTGGTG CTTCTTCCGGTCCGGTTCTGCTAC TGGTGTGCTGACCACGGTCACTGC ACCCGTTGGCCGTGGGTGTGTCCA CCACAAGGTTGGGGT (SEQ ID NO: 628) | 1K | C |

| | | | | |
|------------------------------------|---|--|----|---|
| 2X mTN8-19-33 | FC-5G-AQ- PESQGHCTRWPW MCPPQGWGLEGS GSATGGSGSTASS SGSATGPESQG HCTRWPWMCP QGWGLE (SEQ ID NO: 629) | CCAGAATCTCAAGGTCATTGTACTC GTTGGCCATGGATGTGTCCACCAC AAGGTTGGGGTCTCGAGGGTTCCG GTTCCGCTACCGGCGGCTCTGGCTC CACTGCTTCTTCGGTTCCGGTTCT GCTACTGGTCCGGAATCCCAGGGT CACTGCACCCGTTGGCCGTGGATG TGCCCGCCGCAGGGTTGGGGTCTG GAA (SEQ ID NO: 630) | 1K | C |
| 2X mTN8-19-33 ST-GG del2x LE | FC-5G-AQ- PESQGHCTRWPW MCPPQGWGGSGS ATGGSGGGASSG SGSATGPESQGH CTRWPWMCP PQGWG (SEQ ID NO: 631) | CCAGAATCTCAAGGTCATTGTACTC GTTGGCCATGGATGTGTCCACCAC AAGGTTGGGGTGGTTCCGGTTCCG CTACCGGCGGCTCTGGCGGTGGTG CTTCTTCCGGTTCCGGTTCTGCTAC TGGTCCGGAATCCCAGGGTCACTG CACCCGTTGGCCGTGGATGTGTCC ACCACAAGGTTGGGGT (SEQ ID NO: 632) | 1K | C |

Example 7

In vitro screening of affinity matured peptibodies

- 5 The following exemplary peptibodies were screened according to the protocols set forth above to obtain the following K_D and IC_{50} values. Table VII shows the range of K_D values for selected affinity matured peptibodies compared with the parent peptibodies, as determined by KinExA™ solution based assays or BIAcore® assays. These values demonstrate increased binding affinity of the affinity matured peptibodies for myostatin compared with the parent
- 10 peptibodies. Table VIII shows IC_{50} values for a number of affinity matured peptibodies. A range of values is given in this table.

TABLE VII

| peptibodies | K_D |
|--------------------|--------|
| TN8-19 (parent) | > 1 nM |
| 2xmTN8-19 (parent) | > 1 nM |
| 1x mTN8-19-7 | 10 pM |
| 2x mTN8-19-7 | 12 pM |
| 1x mTN8-19-21 | 6 pM |
| 2x mTN8-19-21 | 6 pM |
| 1x mTN8-19-32 | 9 pM |
| 1x mTN8-19-33 | 21 pM |
| 2x mTN8-19-33 | 3 pM |
| 1x mTN8-19-22 | 4 pM |
| 1x mTN8-19-con1 | 20 pM |

TABLE VIII

| Affinity Matured Peptibody | IC ₅₀ (nM) |
|----------------------------|-----------------------|
| mTN8-19 Con1 | 1.0 – 4.4 |
| mTN8-19-2 | 7.508-34.39 |
| mTN8-19-4 | 16.74 |
| mTN8-19-5 | 7.743 – 3.495 |
| mTN8-19-6 | 17.26 |
| mTN8-19-7 | 1.778 |
| mTN8-19-9 | 22.96-18.77 |
| mTN8-19-10 | 5.252 - 7.4 |
| mTN8-19-11 | 28.66 |
| mTN8-19-12 | 980.4 |
| mTN8-19-13 | 20.04 |
| mTN8-19-14 | 4.065 – 6.556 |
| mTN8-19-16 | 4.654 |
| mTN8-19-21 | 2.767-3.602 |
| mTN8-19-22 | 1.927-3.258 |
| mTN8-19-23 | 6.584 |
| mTN8-19-24 | 1.673-2.927 |
| mTN8-19-27 | 4.837-4.925 |
| mTN8-19-28 | 4.387 |
| mTN8-19-29 | 6.358 |
| mTN8-19-32 | 1.842-3.348 |
| mTN8-19-33 | 2.146-2.745 |
| mTN8-19-34 | 5.028 – 5.069 |
| mTN8Con6-3 | 86.81 |
| mTN8Con6-5 | 2385 |
| mTN8-19-7(-LE) | 1.75-2.677 |
| mTN8-19-21(-LE) | 2.49 |
| mTN8-19-33(-LE) | 1.808 |
| 2xmTN8-19-7 | 0.8572 -2.649 |
| 2xmTN8-19-9 | 1.316-1.228 |
| 2xmTN8-19-14 | 1.18-1.322 |
| 2xmTN8-19-16 | 0.9903 -1.451 |
| 2xmTN8-19-21 | 0.828 -1.434 |
| 2xmTN8-19-22 | 0.9937-1.22 |
| 2xmTN8-19-27 | 1.601-3.931 |
| 2xmTN8-19-7(-LE) | 1.077-1.219 |
| 2xmTN8-19-21(-LE) | 0.8827-1.254 |
| 2xmTN8-19-33(-LE) | 1.12-1.033 |
| mL2-7 | 90.24 |
| mL2-9 | 105.5 |
| mL15-7 | 32.75 |
| mL15-9 | 354.2 |
| mL20-2 | 122.6 |
| mL20-3 | 157.9 |
| mL20-4 | 160 |

Example 8

In vivo Anabolic Activity of Exemplary Peptibodies

The CD1 nu/nu mouse model (Charles River Laboratories, Massachusetts) was used to determine the *in vivo* efficacy of the peptibodies of the present invention which included the human Fc region (huFc). This model responded to the inhibitors of the present invention with a rapid anabolic response which was associated with increased dry muscle mass and an increase in myofibrillar proteins but was not associated with accumulation in body water content.

In one example, the efficacy of 1x peptibody mTN8-19-21 *in vivo* was demonstrated by the following experiment. A group of 10 8 week old CD1 nu/nu mice were treated twice weekly or once weekly with dosages of 1mg/kg, 3 mg/kg and 10 mg/kg (subcutaneous injection). The control group of 10 8 week old CD1 nu/nu mice received a twice weekly (subcutaneous) injection of huFc (vehicle) at 10 mg/kg. The animals were weighed every other day and lean body mass determined by NMR on day 0 and day 13. The animals are then sacrificed at day 14 and the size of the gastrocnemius muscle determined. The results are shown in Figures 2 and 3. Figure 2 shows the increase in total body weight of the mice over 14 days for the various dosages of peptibody compared with the control. As can be seen from Figure 2 all of the dosages have show an increase in body weight compared with the control, with all of the dosages showing statistically significant increases over the control by day 14. Figure 3 shows the change in lean body mass on day 0 and day 13 as determined by NMR, as well as the change in weight of the gastrocnemius muscle dissected from the animals at day 14.

In another example, the 1x mTN8-19-32 peptibody was administered to CD1 nu/nu mice in a biweekly injection of 1 mg/kg, 3 mg/kg, 10 mg/kg, and 30 mg/kg compared with the huFc control (vehicle). The peptibody- treated animals show an increase in total body weight (not shown) as well as lean body mass on day 13 compared with day 0 as determined by NMR measurement. The increase in lean body mass is shown in Figure 4.

In another example, a 1x affinity-matured peptibody was compared with a 2x affinity-matured peptibody for *in vivo* anabolic efficacy. CD1 nu/nu male mice (10 animals per group) were treated with twice weekly injections of 1 mg/kg and 3 mg/kg of 1x mTN8-19-7 and 2x mTN8-19-7 for 35 days, while the control group (10 animals) received twice weekly injections of huFc (3 mg/kg). As shown in Figure 5, treatment with the 2x peptibody resulted in a greater body weight gain and leans carcass weight at necropsy compared with the 1x peptibody or control.

Example 9

Increase in muscular strength

Normal age-matched male 4 month old male C57B/6 mice were treated for 30 days with 2 injections per week subcutaneous injections 5 mg/kg per week of 2x mTN8-19-33, 2x mTN8-19-7, and huFc vehicle control group (10 animals/group). The animals were allowed to recover without any further injections. Gripping strength was measured on day 18 of the recovery period. Gripping strength was measured using a Columbia Instruments meter, model 1027 dsm (Columbus, Ohio). Peptibody treatment resulted in significant increase in gripping strength, with 2x mTN8-19-33 pretreated animals showing a 14 % increase in gripping strength compared with the control-treated mice, while 2x mTN8-19-7 showed a 15% increase in gripping strength compared with the control treated mice.

Example 10

Pharmacokinetics

In vivo pharmacokinetics experiments were performed using representative peptibodies without the LE sequences. 10 mg/kg and 5mg/kg dosages were administered to CD1 nu/nu mice and the following parameters determined: C_{max} (ug/mL), area under the curve (AUC) (ug-hr/mL), and half-life (hr). It was found that the 2x versions of the affinity matured peptibodies have a significantly longer half-life than the 1x versions. For example 1x affinity matured mTN8-19-22 has a half-life in the animals of about 50.2 hours, whereas 2x mTN8-19-22 has a half-life of about 85.2 hours. Affinity matured 1x mTN8-7 has a half-life of about 65 hours, whereas 2x mTN8-19-7 has a half-life of about 106 hours.

Example 11

Treatment of *mdx* Mice

The peptibodies of the present invention have been shown to increase lean muscle mass in an animal and are useful for the treatment of a variety of disorders which involve muscle wasting. Muscular dystrophy is one of those disorders. The mouse model for Duchenne's muscular dystrophy is the Duchenne *mdx* mouse (Jackson Laboratories, Bar Harbor, Maine). Aged (10 month old) *mdx* mice were injected with either the peptibody 1x mTN8-19-33 (n=8/group) or with the vehicle huFc protein (N=6/group) for a three month period of time. The dosing schedule was every other day, 10 mg/kg, by subcutaneous injection. The peptibody treatment had a positive effect on increasing and maintaining body mass for the aged *mdx* mice. Significant increases in body weight were observed in the peptibody-treated group compared to the hu-Fc-treated control group, as shown in Figure 6A. In addition, NMR analysis revealed that the lean body mass to fat

mass ratio was also significantly increased in the aged *mdx* mice as a result of the peptibody treatment compared with the control group, and that the fat percentage of body weight decreased in the peptibody treated mice compared with the control group, as shown in Figure 6B.

5

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

10

CLAIMS

What is claimed is:

1. A binding agent comprising at least one peptide capable of binding myostatin, wherein the peptide comprises the amino acid sequence WMCPP (SEQ ID NO: 633), and physiologically acceptable salts thereof.
2. The binding agent of claim 1, wherein the peptide is between 5 and 50 amino acids in length.
3. A binding agent comprising at least one peptide capable of binding myostatin, wherein the peptide comprises the amino acid sequence C_{a1}a₂W_{a3}WMCPP (SEQ ID NO: 352), wherein a₁, a₂ and a₃ are selected from a neutral hydrophobic, neutral polar, or basic amino acid, and wherein the peptide is between 10 and 50 amino acids in length, and physiologically acceptable salts thereof.
4. A binding agent comprising at least one peptide capable of binding myostatin, wherein the peptide comprises the sequence C_{b1}b₂W_{b3}WMCPP (SEQ ID NO: 353), wherein
 - b₁ is selected from any one of the amino acids T, I, or R;
 - b₂ is selected from any one of R, S, Q;
 - b₃ is selected from any one of P, R and Q,
 and wherein the peptide is between 10 and 50 amino acids in length, and physiologically acceptable salts thereof.
5. A binding agent comprising at least one peptide capable of binding myostatin, wherein the peptide comprises the sequence c₁c₂c₃c₄c₅c₆Cc₇c₈Wc₉WMCPPc₁₀c₁₁c₁₂c₁₃ (SEQ ID NO: 354), wherein:
 - c₁ is absent or any amino acid;
 - c₂ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 - c₃ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 - c₄ is absent or any amino acid;
 - c₅ is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 - c₆ is absent or a neutral hydrophobic, neutral polar, or basic amino acid;
 - c₇ is a neutral hydrophobic, neutral polar, or basic amino acid;
 - c₈ is a neutral hydrophobic, neutral polar, or basic amino acid;
 - c₉ is a neutral hydrophobic, neutral polar or basic amino acid; and
 - c₁₀ to c₁₃ is any amino acid; and wherein the peptide is between 20 and 50 amino acids in length, and physiologically acceptable salts thereof.

6. A binding agent comprising at least one peptide capable of binding myostatin, wherein the peptide comprises the sequence

$d_1d_2d_3d_4d_5d_6Cd_7d_8Wd_9WMCPPd_{10}d_{11}d_{12}d_{13}$ (SEQ ID NO: 355), wherein

d_1 is absent or any amino acid;

d_2 is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

d_3 is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

d_4 is absent or any amino acid;

d_5 is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;

d_6 is absent or a neutral hydrophobic, neutral polar, or basic amino acid;

d_7 is selected from any one of the amino acids T, I, or R;

d_8 is selected from any one of R, S, Q;

d_9 is selected from any one of P, R and Q, and

d_{10} to d_{13} is selected from any amino acid,

and wherein the peptide is between 20 and 50 amino acids in length, and physiologically acceptable salts thereof.

7. A binding agent comprising at least one peptide capable of binding myostatin, wherein the peptide comprises the sequence $WYe_1e_2Ye_3G$, (SEQ ID NO: 356)

wherein e_1 is P, S or Y,

e_2 is C or Q, and

e_3 is G or H, and wherein the peptide is between 7 and 50 amino acids in length, and physiologically acceptable salts thereof.

8. A binding agent comprising at least one peptide capable of binding myostatin, wherein the peptide comprises the sequence $f_1EMLf_2SLf_3f_4LL$, (SEQ ID NO: 455), wherein f_1 is M or I,

f_2 is any amino acid,

f_3 is L or F,

f_4 is E, Q or D;

and wherein the peptide is between 7 and 50 amino acids in length, and physiologically acceptable salts thereof.

9. A binding agent comprising at least one peptide capable of binding myostatin, wherein the peptide comprises the sequence $Lg_1g_2LLg_3g_4L$, (SEQ ID NO: 456), wherein

g_1 is Q, D or E,

g_2 is S, Q, D or E,

g_3 is any amino acid,

g_4 is L, W, F, or Y, and wherein the peptide is between 8 and 50 amino acids in length, and physiologically acceptable salts thereof.

10. A binding agent comprising at least one peptide capable of binding myostatin, wherein the peptide comprises the sequence $h_1h_2h_3h_4h_5h_6h_7h_8h_9$ (SEQ ID NO: 457), wherein

h_1 is R or D,
 h_2 is any amino acid,
 h_3 is A, T S or Q,
 h_4 is L or M,
 h_5 is L or S,
 h_6 is any amino acid,
 h_7 is F or E,
 h_8 is W, F or C,
 h_9 is L, F, M or K, and wherein the peptide is between 9 and 50 amino acids in length, and physiologically acceptable salts thereof.

11. A binding agent wherein said agent has the structure:

$(X^1)_a-F^1-(X^2)_b$, or multimers thereof;

wherein F^1 is a vehicle; and X^1 and X^2 are each independently selected from

$-(L^1)_c-P^1$;

$-(L^1)_c-P^1-(L^2)_d-P^2$;

$-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$;

and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$;

wherein P^1 , P^2 , P^3 , and P^4 are peptides capable of binding myostatin, and each independently comprise the amino acid sequence WMCPP (SEQ ID NO: 633);

wherein L^1 , L^2 , L^3 , and L^4 are each linkers;

and a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1, and physiologically acceptable salts thereof.

12. The binding agent of claim 11 wherein one or more of the myostatin binding peptides comprise the amino acid sequence $\underline{Ca_1a_2Wa_3WMCPP}$ (SEQ ID NO: 352), wherein a_1 , a_2 and a_3 are selected from a neutral hydrophobic, neutral polar, or basic amino acid, and wherein the peptide is between 10 and 50 amino acids in length, and physiologically acceptable salts thereof.

13. The binding agent of claim 11, wherein one or more of the myostatin binding peptides each independently comprise the amino acid sequence $\underline{Cb_1b_2Wb_3WMCPP}$ (SEQ ID NO: 353), wherein

b_1 is selected from any one of the amino acids T, I, or R;
 b_2 is selected from any one of R, S, Q;
 b_3 is selected from any one of P, R and Q,

and wherein the peptide is between 10 and 50 amino acids in length, and physiologically acceptable salts thereof.

14. The binding agent of claim 11, wherein one or more of the myostatin binding peptides each independently comprise the sequence $c_1c_2c_3c_4c_5c_6Cc_7c_8Wc_9WMCPPc_{10}c_{11}c_{12}c_{13}$ (SEQ ID NO: 354), wherein:

c_1 is absent or any amino acid;
 c_2 is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 c_3 is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 c_4 is absent or any amino acid;
 c_5 is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 c_6 is absent or a neutral hydrophobic, neutral polar, or basic amino acid;
 c_7 is a neutral hydrophobic, neutral polar, or basic amino acid;
 c_8 is a neutral hydrophobic, neutral polar, or basic amino acid;
 c_9 is a neutral hydrophobic, neutral polar or basic amino acid; and
 c_{10} to c_{13} is any amino acid; and wherein the peptide is between 20 and 50 amino acids in length, and physiologically acceptable salts thereof..

15. The binding agent of claim 11, wherein one or more of the myostatin binding peptides each independently comprise the sequence $d_1d_2d_3d_4d_5d_6Cd_7d_8Wd_9WMCPPd_{10}d_{11}d_{12}d_{13}$ (SEQ ID NO: 355), wherein

d_1 is absent or any amino acid;
 d_2 is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 d_3 is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 d_4 is absent or any amino acid;
 d_5 is absent or a neutral hydrophobic, neutral polar, or acidic amino acid;
 d_6 is absent or a neutral hydrophobic, neutral polar, or basic amino acid;
 d_7 is selected from any one of the amino acids T, I, or R;
 d_8 is selected from any one of R, S, Q;
 d_9 is selected from any one of P, R and Q, and
 d_{10} to d_{13} is selected from any amino acid,
and wherein the peptide is between 20 and 50 amino acids in length, and physiologically acceptable salts thereof.

16. A binding agent wherein said agent has the structure:

$(X^1)_a-F^1-(X^2)_b$, or multimers thereof;

wherein F^1 is a vehicle; and X^1 and X^2 are each independently selected from

$-(L^1)_c-P^1$;

$-(L^1)_c-P^1-(L^2)_d-P^2$;

$-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$;

and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$;

wherein P^1 , P^2 , P^3 , and P^4 are peptides capable of binding myostatin, and wherein one or more of P^1 , P^2 , P^3 , and P^4 each independently are selected from the group consisting of:

(a) a peptide comprising the amino acid sequence WY e_1 e_2 Y e_3 G, (SEQ ID NO: 356), wherein e_1 is P, S or Y, e_2 is C or Q, and e_3 is G or H;

(b) a peptide comprising the amino acid sequence f_1 EML f_2 SL f_3 f_4 LL, (SEQ ID NO: 455), wherein f_1 is M or I, f_2 is any amino acid, f_3 is L or F, and f_4 is E, Q or D;

(c) a peptide comprising the amino acid sequence L g_1 gLL g_3 g_4 L, (SEQ ID NO: 456), wherein g_1 is Q, D or E, g_2 is S, Q, D or E, g_3 is any amino acid, and g_4 is L, W, F, or Y; and

(d) a peptide comprising the amino acid sequence $h_1h_2h_3h_4h_5h_6h_7h_8h_9$ (SEQ ID NO: 457), wherein h_1 is R or D, h_2 is any amino acid, h_3 is A, T S or Q, h_4 is L or M, h_5 is L or S, h_6 is any amino acid, h_7 is F or E, h_8 is W, F or C, and h_9 is L, F, M or K;

wherein the peptide is between 9 and 50 amino acids in length,

wherein L^1 , L^2 , L^3 , and L^4 are each linkers;

and a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1, and physiologically acceptable salts thereof.

17. A binding agent wherein said agent has the structure:

$(X^1)_a-F^1-(X^2)_b$, or multimers thereof;

wherein F^1 is a vehicle; and X^1 and X^2 are each independently selected from

$-(L^1)_c-P^1$;

$-(L^1)_c-P^1-(L^2)_d-P^2$;

$-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$;

and $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$;

wherein P^1 , P^2 , P^3 , and P^4 are peptides capable of binding myostatin, and are independently selected from SEQ ID NO: 305 through 351 and SEQ ID NO: 357 through 454;

wherein L^1 , L^2 , L^3 , and L^4 are each linkers;

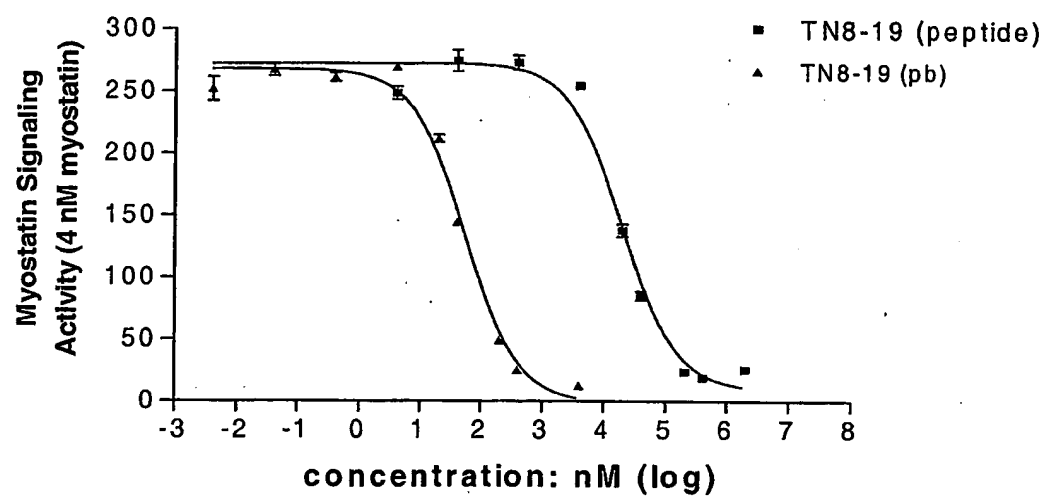
and a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1, and physiologically acceptable salts thereof.

18. The binding agent of any one of claims 11 through 17, wherein the vehicle is an Fc domain.

19. A polynucleotide sequence encoding the binding agent of claim 18.

20. An expression vector comprising the polynucleotide of claim 19.
21. A host cell comprising the expression vector of claim 20.
22. The host cell of claim 21, wherein the cell is a procaryotic cell.
23. The host cell of claim 21, wherein the cell is a eucaryotic cell.
24. A pharmaceutical composition comprising an effective amount of the binding agent of any one of claims 1 or 11 in admixture with a pharmaceutically acceptable carrier thereof.
25. The pharmaceutical composition of claim 24, wherein the vehicle is an Fc domain.
26. A method of inhibiting myostatin activity in a subject comprising administering an effective amount of the binding agent of any one of claims 1, 3 or 11 to the subject.
27. A method of increasing lean muscle mass in a subject comprising administering the composition of claim 24 to the subject.
28. The method of claim 27, wherein the subject is a food animal.
29. A method of increasing the ratio of lean muscle mass to fat in a subject comprising administering a therapeutically effective amount of the composition of claim 24 to the subject.
30. A method of treating a muscle-wasting disease in a subject comprising administering a therapeutically effective amount of the composition of claim 24 to the subject.
31. The method of claim 30, wherein the disease is selected from muscular dystrophy, amyotrophic lateral sclerosis, congestive obstructive pulmonary disease, chronic heart failure, cancer, AIDs, renal failure, uremia, rheumatoid arthritis, age-related sarcopenia, and muscle-wasting due to prolonged bedrest, spinal chord injury, stroke, bone fracture, and aging.
32. A method of treating a myostatin-related metabolic disorder in a subject comprising administering a therapeutically effective amount of the composition of claim 24 to the subject.

33. The method of claim 32 wherein the metabolic disorder is selected from diabetes, obesity, hyperglycemia, and bone loss.
34. A method of detecting myostatin in a sample comprising contacting the sample with a binding agent of claims 1 or 11, and detecting the bound complex.
35. A method of measuring myostatin in a sample comprising contacting the sample with a binding agent of claims 1 or 11, and measuring the bound complex.
36. A method of diagnosing a myostatin related disorder in a subject comprising contacting a sample taken from the subject with a binding agent of claims 1 or 11, and detecting the bound complex.

**FIGURE 1**

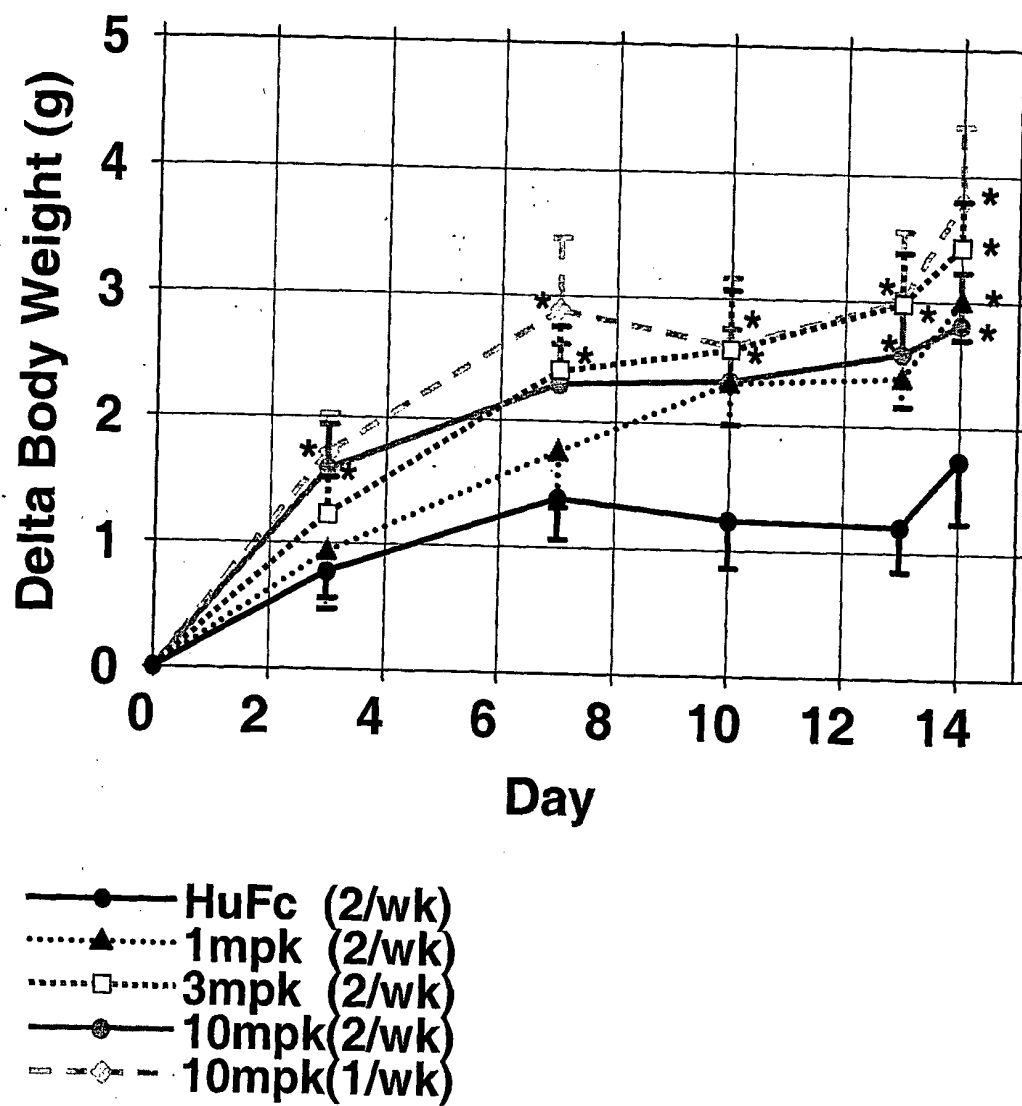


FIGURE 2

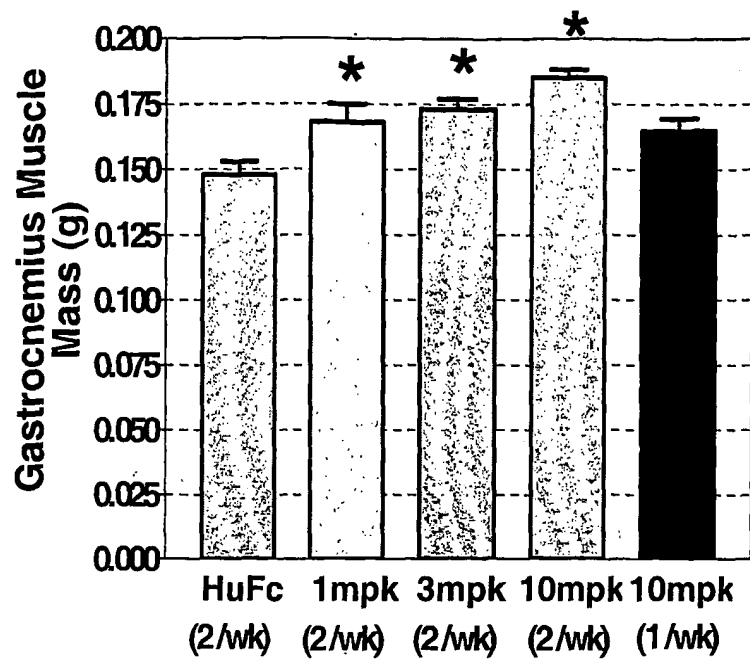


FIGURE 3A

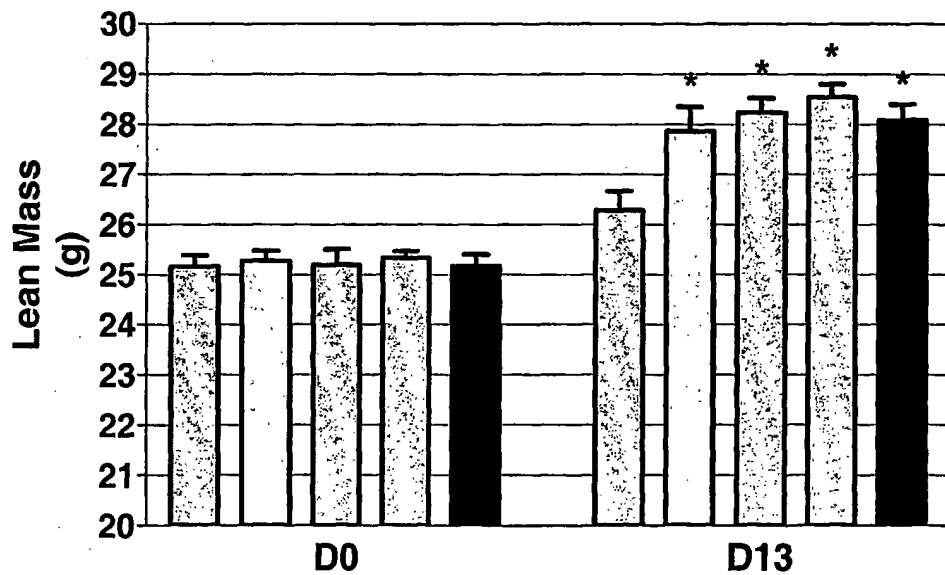
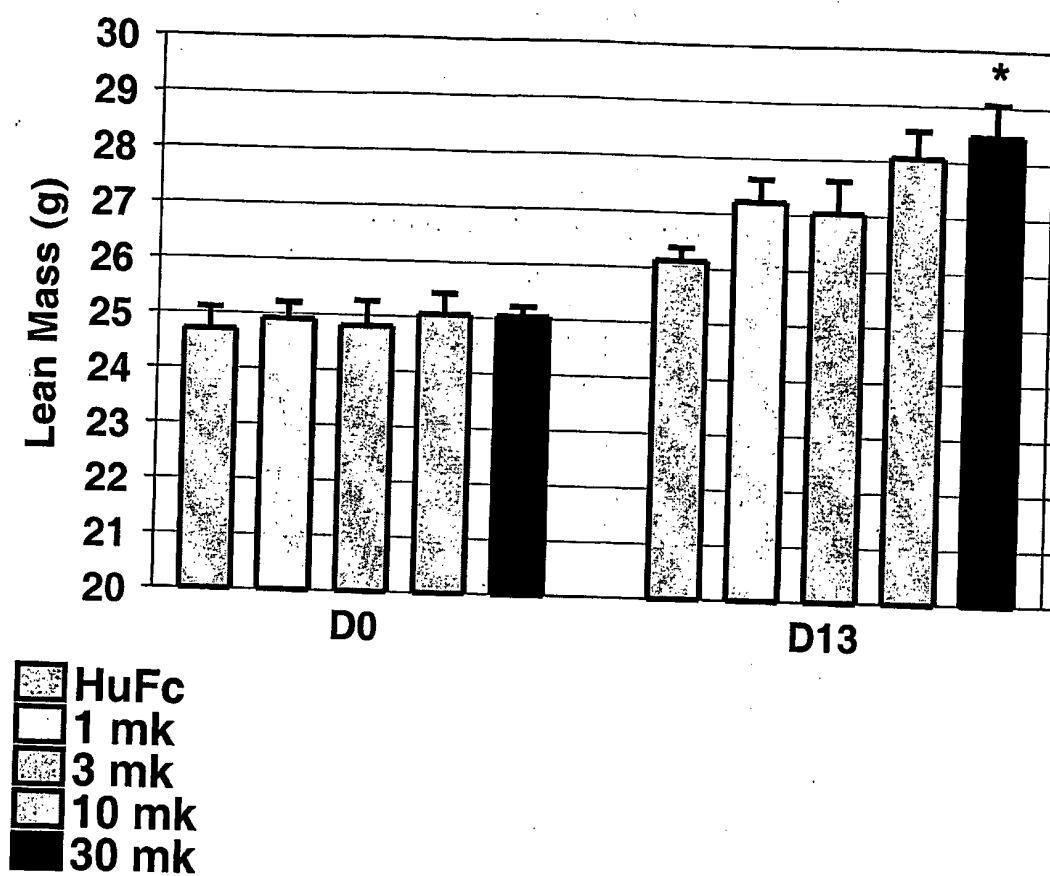


FIGURE 3B

**FIGURE 4**

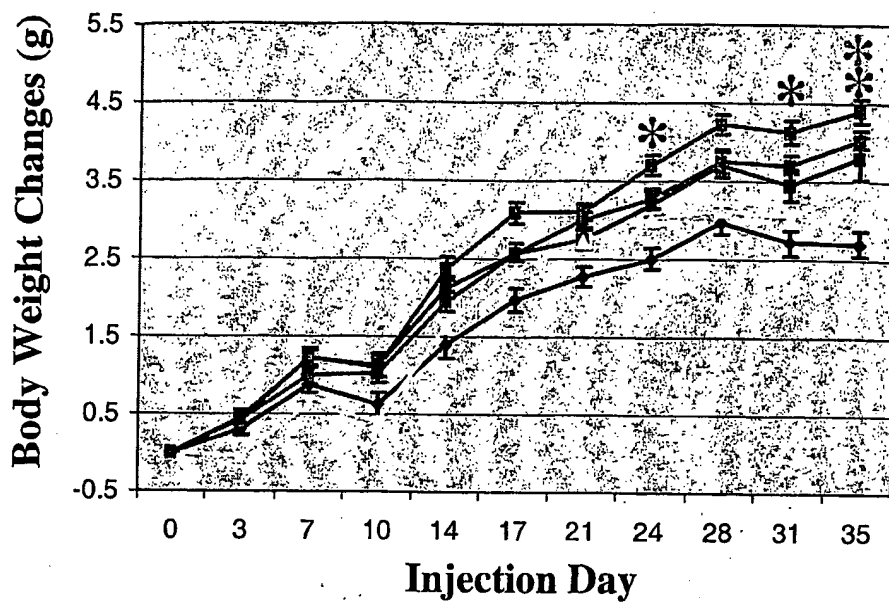


FIGURE 5A

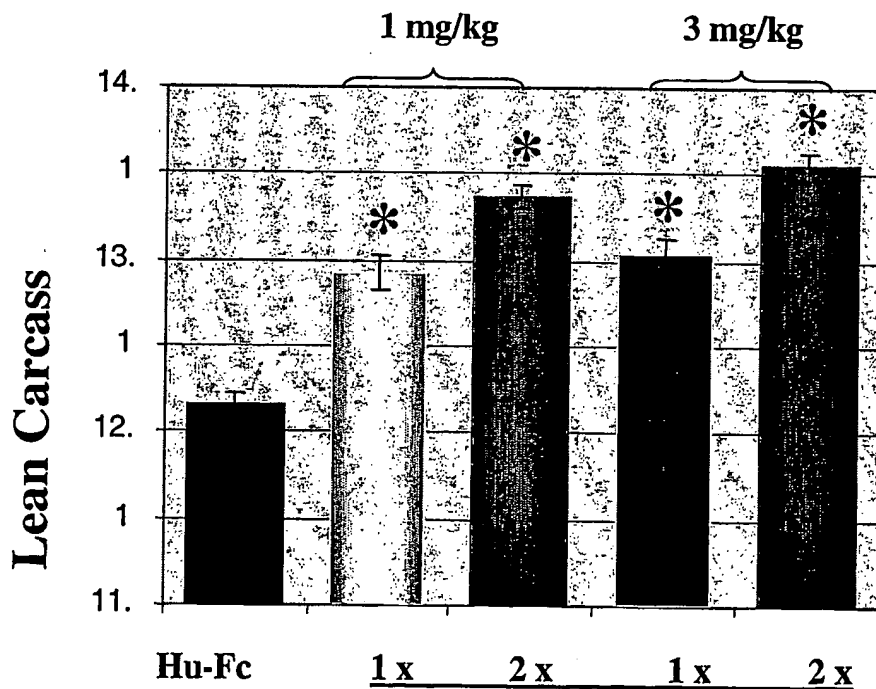
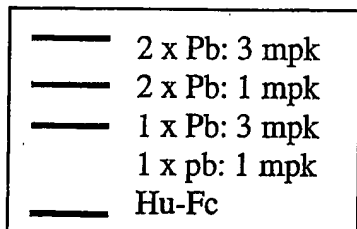
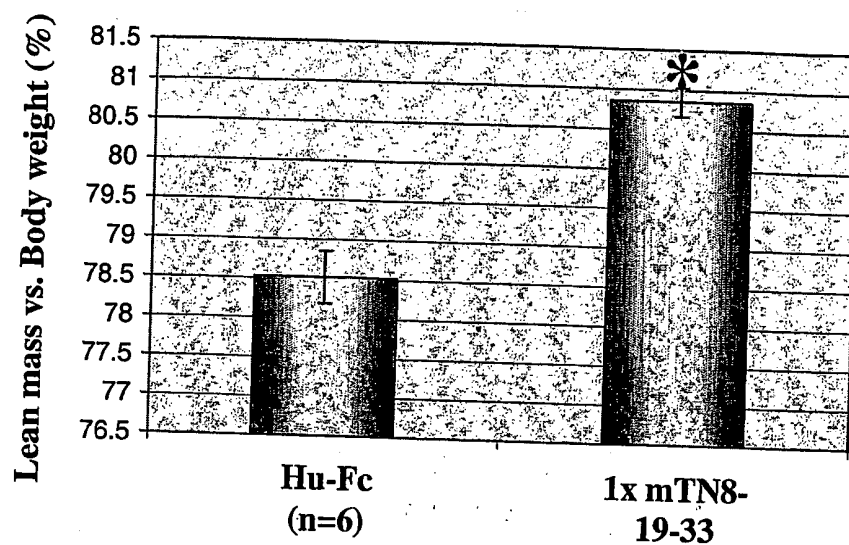
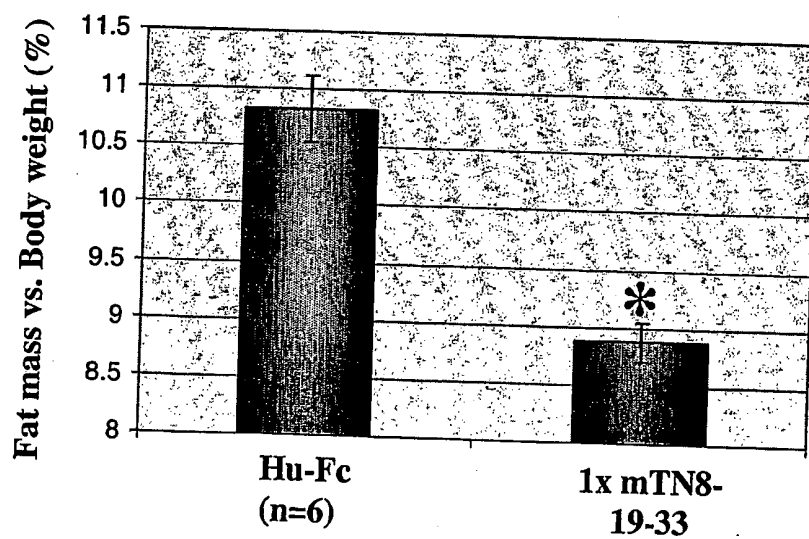


FIGURE 5B



**FIGURE 6A****FIGURE 6B**

SEQUENCE LISTING

<110> AMGEN, INC.
 Han, HQ
 Min, Hosung
 Boone, Thomas Charles

<120> BINDING AGENTS WHICH INHIBIT MYOSTATIN

<130> A-828 (WO)

<140> to-be-assigned

<141> 2003-12-19

<150> US 60/435,923

<151> 2002-12-20

<160> 634

<170> PatentIn version 3.2

<210> 1

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 1 5 10

<210> 58
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 <212> PRT
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Gly Leu

<210> 59
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Trp Phe Arg Cys Val Leu Thr Gly Ile Val Asp Trp Ser Glu Cys Phe
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<211> 18

<212> PRT

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His Ala

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1 5 10 15

Trp Tyr

<210> 68
<211> 18
<212> PRT
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<220>
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<400> 68

Phe Ser Ser Cys Trp Ser Pro Val Ser Arg Gln Asp Met Phe Cys Val
1 5 10 15

Phe Tyr

<210> 69
<211> 17
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<220>
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<400> 69

Ser His Lys Cys Glu Tyr Ser Gly Trp Leu Gln Pro Leu Cys Tyr Arg
1 5 10 15

Pro

<210> 70

<211> 18
 <212> PRT
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<220>
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<400> 70

Pro Trp Trp Cys Gln Asp Asn Tyr Val Gln His Met Leu His Cys Asp
 1 5 10 15

Ser Pro

<210> 71
 <211> 18
 <212> PRT
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<220>
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<400> 71

Trp Phe Arg Cys Met Leu Met Asn Ser Phe Asp Ala Phe Gln Cys Val
 1 5 10 15

Ser Tyr

<210> 72
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<220>
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<400> 72

Pro Asp Ala Cys Arg Asp Gln Pro Trp Tyr Met Phe Met Gly Cys Met
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Leu Gly

<210> 73
 <211> 14
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<400> 73

Phe Leu Ala Cys Phe Val Glu Phe Glu Leu Cys Phe Asp Ser
1 5 10

<210> 74

<211> 18

<212> PRT

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<220>

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<400> 74

Ser Ala Tyr Cys Ile Ile Thr Glu Ser Asp Pro Tyr Val Leu Cys Val
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Pro Leu

<210> 75

<211> 18

<212> PRT

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<400> 75

Pro Ser Ile Cys Glu Ser Tyr Ser Thr Met Trp Leu Pro Met Cys Gln
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His Asn

<210> 76

<211> 18

<212> PRT

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<400> 76

Trp Leu Asp Cys His Asp Asp Ser Trp Ala Trp Thr Lys Met Cys Arg
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Ser His

<210> 77

<211> 18
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<400> 77

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Phe Asn

<210> 78
<211> 18
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<400> 78

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Phe Tyr

<210> 79
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1 5 10 15

Ser Arg

<210> 80
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<220>
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<400> 80

Leu Pro Leu Cys Asn Leu Lys Glu Ile Ser His Val Gln Ala Cys Val
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Leu Phe

<210> 81

<211> 18

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<213> Artificial Sequence

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<400> 81

Ser Pro Glu Cys Ala Phe Ala Arg Trp Leu Gly Ile Glu Gln Cys Gln
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Arg Asp

<210> 82

<211> 18

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<400> 82

Tyr Pro Gln Cys Phe Asn Leu His Leu Leu Glu Trp Thr Glu Cys Asp
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Trp Phe

<210> 83

<211> 18

<212> PRT

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<400> 83

Arg Trp Arg Cys Glu Ile Tyr Asp Ser Glu Phe Leu Pro Lys Cys Trp
1 5 10 15

Phe Phe

<210> 84
<211> 14
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<400> 84

Leu Val Gly Cys Asp Asn Val Trp His Arg Cys Lys Leu Phe
1 5 10

<210> 85
<211> 18
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<400> 85

Ala Gly Trp Cys His Val Trp Gly Glu Met Phe Gly Met Gly Cys Ser
1 5 10 15

Ala Leu

<210> 86
<211> 18
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<220>
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<400> 86

His His Glu Cys Glu Trp Met Ala Arg Trp Met Ser Leu Asp Cys Val
1 5 10 15

Gly Leu

<210> 87
<211> 18
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<220>
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<400> 87

Phe Pro Met Cys Gly Ile Ala Gly Met Lys Asp Phe Asp Phe Cys Val
 1 5 10 15

Trp Tyr

<210> 88

<211> 18

<212> PRT

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<400> 88

Arg Asp Asp Cys Thr Phe Trp Pro Glu Trp Leu Trp Lys Leu Cys Glu
 1 5 10 15

Arg Pro

<210> 89

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

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<400> 89

Tyr Asn Phe Cys Ser Tyr Leu Phe Gly Val Ser Lys Glu Ala Cys Gln
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Leu Pro

<210> 90

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

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<400> 90

Ala His Trp Cys Glu Gln Gly Pro Trp Arg Tyr Gly Asn Ile Cys Met
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Ala Tyr

<210> 91
<211> 18
<212> PRT
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<400> 91

Asn Leu Val Cys Gly Lys Ile Ser Ala Trp Gly Asp Glu Ala Cys Ala
1 5 10 15

Arg Ala

<210> 92
<211> 18
<212> PRT
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<220>
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<400> 92

His Asn Val Cys Thr Ile Met Gly Pro Ser Met Lys Trp Phe Cys Trp
1 5 10 15

Asn Asp

<210> 93
<211> 18
<212> PRT
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<220>
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<400> 93

Asn Asp Leu Cys Ala Met Trp Gly Trp Arg Asn Thr Ile Trp Cys Gln
1 5 10 15

Asn Ser

<210> 94
<211> 18
<212> PRT
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<220>

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<400> 94

Pro Pro Phe Cys Gln Asn Asp Asn Asp Met Leu Gln Ser Leu Cys Lys
 1 5 10 15

Leu Leu

<210> 95

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

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<400> 95

Trp Tyr Asp Cys Asn Val Pro Asn Glu Leu Leu Ser Gly Leu Cys Arg
 1 5 10 15

Leu Phe

<210> 96

<211> 18

<212> PRT

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<220>

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<400> 96

Tyr Gly Asp Cys Asp Gln Asn His Trp Met Trp Pro Phe Thr Cys Leu
 1 5 10 15

Ser Leu

<210> 97

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

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<400> 97

Gly Trp Met Cys His Phe Asp Leu His Asp Trp Gly Ala Thr Cys Gln

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5

10

15

Pro Asp

<210> 98

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 98

Tyr Phe His Cys Met Phe Gly Gly His Glu Phe Glu Val His Cys Glu
1 5 10 15

Ser Phe

<210> 99

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

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<400> 99

Ala Tyr Trp Cys Trp His Gly Gln Cys Val Arg Phe
1 5 10

<210> 100

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 100

Ser Glu His Trp Thr Phe Thr Asp Trp Asp Gly Asn Glu Trp Trp Val
1 5 10 15

Arg Pro Phe

<210> 101

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 101

Met Glu Met Leu Asp Ser Leu Phe Glu Leu Leu Lys Asp Met Val Pro
1 5 10 15

Ile Ser Lys Ala
20

<210> 102

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 102

Ser Pro Pro Glu Glu Ala Leu Met Glu Trp Leu Gly Trp Gln Tyr Gly
1 5 10 15

Lys Phe Thr

<210> 103

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 103

Ser Pro Glu Asn Leu Leu Asn Asp Leu Tyr Ile Leu Met Thr Lys Gln
1 5 10 15

Glu Trp Tyr Gly
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<210> 104

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 104

Phe His Trp Glu Glu Gly Ile Pro Phe His Val Val Thr Pro Tyr Ser

1 5 10 15

Tyr Asp Arg Met
20

<210> 105
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<400> 105

Lys Arg Leu Leu Glu Gln Phe Met Asn Asp Leu Ala Glu Leu Val Ser
1 5 10 15

Gly His Ser

<210> 106
<211> 20
<212> PRT
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<220>
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<400> 106

Asp Thr Arg Asp Ala Leu Phe Gln Glu Phe Tyr Glu Phe Val Arg Ser
1 5 10 15

Arg Leu Val Ile
20

<210> 107
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 107

Arg Met Ser Ala Ala Pro Arg Pro Leu Thr Tyr Arg Asp Ile Met Asp
1 5 10 15

Gln Tyr Trp His
20

<210> 108
<211> 20
<212> PRT
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<220>
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<400> 108

Asn Asp Lys Ala His Phe Phe Glu Met Phe Met Phe Asp Val His Asn
1 5 10 15

Phe Val Glu Ser
20

<210> 109
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Myostatin Binding Peptide

<400> 109

Gln Thr Gln Ala Gln Lys Ile Asp Gly Leu Trp Glu Leu Leu Gln Ser
1 5 10 15

Ile Arg Asn Gln
20

<210> 110
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 110

Met Leu Ser Glu Phe Glu Glu Phe Leu Gly Asn Leu Val His Arg Gln
1 5 10 15

Glu Ala

<210> 111
<211> 20
<212> PRT
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<220>
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<400> 111

Tyr Thr Pro Lys Met Gly Ser Glu Trp Thr Ser Phe Trp His Asn Arg
 1 5 10 15

Ile His Tyr Leu
 20

<210> 112

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 112

Leu Asn Asp Thr Leu Leu Arg Glu Leu Lys Met Val Leu Asn Ser Leu
 1 5 10 15

Ser Asp Met Lys
 20

<210> 113

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

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<400> 113

Phe Asp Val Glu Arg Asp Leu Met Arg Trp Leu Glu Gly Phe Met Gln
 1 5 10 15

Ser Ala Ala Thr
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<210> 114

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 114

His His Gly Trp Asn Tyr Leu Arg Lys Gly Ser Ala Pro Gln Trp Phe
 1 5 10 15

Glu Ala Trp Val
20

<210> 115
<211> 20
<212> PRT
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<220>
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<400> 115

Val Glu Ser Leu His Gln Leu Gln Met Trp Leu Asp Gln Lys Leu Ala
1 5 10 15

Ser Gly Pro His
20

<210> 116
<211> 18
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<220>
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<400> 116

Arg Ala Thr Leu Leu Lys Asp Phe Trp Gln Leu Val Glu Gly Tyr Gly
1 5 10 15

Asp Asn

<210> 117
<211> 16
<212> PRT
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<220>
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<400> 117

Glu Glu Leu Leu Arg Glu Phe Tyr Arg Phe Val Ser Ala Phe Asp Tyr
1 5 10 15

<210> 118
<211> 20
<212> PRT
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<220>
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<400> 118

Gly Leu Leu Asp Glu Phe Ser His Phe Ile Ala Glu Gln Phe Tyr Gln
1 5 10 15

Met Pro Gly Gly
20

<210> 119

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 119

Tyr Arg Glu Met Ser Met Leu Glu Gly Leu Leu Asp Val Leu Glu Arg
1 5 10 15

Leu Gln His Tyr
20

<210> 120

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 120

His Asn Ser Ser Gln Met Leu Leu Ser Glu Leu Ile Met Leu Val Gly
1 5 10 15

Ser Met Met Gln
20

<210> 121

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 121

Trp Arg Glu His Phe Leu Asn Ser Asp Tyr Ile Arg Asp Lys Leu Ile
1 5 10 15

Ala Ile Asp Gly
20

<210> 122
<211> 19
<212> PRT
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<220>
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<400> 122

Gln Phe Pro Phe Tyr Val Phe Asp Asp Leu Pro Ala Gln Leu Glu Tyr
1 5 10 15

Trp Ile Ala

<210> 123
<211> 20
<212> PRT
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<220>
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<400> 123

Glu Phe Phe His Trp Leu His Asn His Arg Ser Glu Val Asn His Trp
1 5 10 15

Leu Asp Met Asn
20

<210> 124
<211> 19
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<220>
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<400> 124

Glu Ala Leu Phe Gln Asn Phe Phe Arg Asp Val Leu Thr Leu Ser Glu
1 5 10 15

Arg Glu Tyr

<210> 125
<211> 20
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<220>

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<400> 125

Gln Tyr Trp Glu Gln Gln Trp Met Thr Tyr Phe Arg Glu Asn Gly Leu
1 5 10 15

His Val Gln Tyr
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<210> 126

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 126

Asn Gln Arg Met Met Leu Glu Asp Leu Trp Arg Ile Met Thr Pro Met
1 5 10 15

Phe Gly Arg Ser
20

<210> 127

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 127

Phe Leu Asp Glu Leu Lys Ala Glu Leu Ser Arg His Tyr Ala Leu Asp
1 5 10 15

Asp Leu Asp Glu
20

<210> 128

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 128

Gly Lys Leu Ile Glu Gly Leu Leu Asn Glu Leu Met Gln Leu Glu Thr
 1 5 10 15

Phe Met Pro Asp
 20

<210> 129
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 129

Ile Leu Leu Leu Asp Glu Tyr Lys Lys Asp Trp Lys Ser Trp Phe
 1 5 10 15

<210> 130
 <211> 50
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Myostatin Binding Peptide

<400> 130

Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Tyr Gly Ser
 1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 20 25 30

Ser Ala Thr Gly Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro
 35 40 45

Pro Tyr
 50

<210> 131
 <211> 43
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 131

Trp Tyr Pro Cys Tyr Glu Gly His Phe Trp Cys Tyr Asp Leu Gly Ser
 1 5 10 15

Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Trp Tyr Pro
 20 25 30

Cys Tyr Glu Gly His Phe Trp Cys Tyr Asp Leu
 35 40

<210> 132
 <211> 50
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 132

His Thr Pro Cys Pro Trp Phe Ala Pro Leu Cys Val Glu Trp Gly Ser
 1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 20 25 30

Ser Ala Thr Gly His Thr Pro Cys Pro Trp Phe Ala Pro Leu Cys Val
 35 40 45

Glu Trp
 50

<210> 133
 <211> 50
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 133

Pro Asp Trp Cys Ile Asp Pro Asp Trp Trp Cys Lys Phe Trp Gly Ser
 1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 20 25 30

Ser Ala Thr Gly Pro Asp Trp Cys Ile Asp Pro Asp Trp Trp Cys Lys
 35 40 45

Phe Trp
 50

<210> 134
 <211> 50
 <212> PRT
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<220>
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<400> 134

Ala Asn Trp Cys Val Ser Pro Asn Trp Phe Cys Met Val Met Gly Ser
 1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 20 25 30

Ser Ala Thr Gly Ala Asn Trp Cys Val Ser Pro Asn Trp Phe Cys Met
 35 40 45

Val Met
 50

<210> 135
 <211> 50
 <212> PRT
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<220>
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<400> 135

Pro Asp Trp Cys Ile Asp Pro Asp Trp Trp Cys Lys Phe Trp Gly Ser
 1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 20 25 30

Ser Ala Thr Gly Pro Asp Trp Cys Ile Asp Pro Asp Trp Trp Cys Lys
 35 40 45

Phe Trp
 50

<210> 136
 <211> 50
 <212> PRT
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<220>
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<400> 136

His Trp Ala Cys Gly Tyr Trp Pro Trp Ser Cys Lys Trp Val Gly Ser
 1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 20 25 30

Ser Ala Thr Gly His Trp Ala Cys Gly Tyr Trp Pro Trp Ser Cys Lys
 35 40 45

Trp Val
 50

<210> 137
 <211> 50
 <212> PRT
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<220>
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<400> 137

Lys Lys His Cys Gln Ile Trp Thr Trp Met Cys Ala Pro Lys Gly Ser
 1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 20 25 30

Ser Ala Thr Gly Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro
 35 40 45

Pro Tyr
 50

<210> 138
 <211> 50
 <212> PRT
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<220>
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<400> 138

Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Tyr Gly Ser
 1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 20 25 30

Ser Ala Thr Gly Lys Lys His Cys Gln Ile Trp Thr Trp Met Cys Ala
 35 40 45

Pro Lys
 50

<210> 139
 <211> 50
 <212> PRT
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<220>
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<400> 139

Lys Lys His Cys Gln Ile Trp Thr Trp Met Cys Ala Pro Lys Gly Ser
 1 5 10 15

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 20 25 30

Ser Ala Thr Gly Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro
 35 40 45

Pro Tyr
 50

<210> 140
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 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 140

Lys Lys His Cys Gln Ile Trp Thr Trp Met Cys Ala Pro Lys Gly Gly
 1 5 10 15

Gly Gly Gly Gly Gly Gly Gln Gly His Cys Thr Arg Trp Pro Trp Met
 20 25 30

Cys Pro Pro Tyr
 35

<210> 141
 <211> 34
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 141

Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Tyr Gly Gly
1 5 10 15

Gly Gly Gly Gly Lys Lys His Cys Gln Ile Trp Thr Trp Met Cys Ala
20 25 30

Pro Lys

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<210> 142
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<400> 142

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<210> 143
<211> 14
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<220>
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<400> 143

Trp Xaa Xaa Cys Xaa Xaa Xaa Gly Phe Trp Cys Leu Asn Val
 1 5 10

<210> 144
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<400> 144

Ile Xaa Gly Cys Xaa Trp Trp Asp Xaa Xaa Cys Tyr Xaa Xaa
 1 5 10

<210> 145
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 <223> Xaa = any amino acid

<400> 145

Xaa Xaa Trp Cys Val Ser Pro Xaa Trp Phe Cys Xaa Xaa Xaa
 1 5 10

<210> 146
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<400> 146

Xaa Xaa Xaa Cys Pro Trp Phe Ala Xaa Xaa Cys Val Asp Trp
 1 5 10

<210> 147
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<220>
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<400> 147
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42

<210> 148
 <211> 42
 <212> DNA
 <213> Artificial Sequence

<220>
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<400> 148

aaagacctgt gcgctatgtg gcactggatg tgcaaaccgc cg 42

<210> 149
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 149
aaagacctgt gcaaaatgtg gaaatggatg tgcaaaccgc cg 42

<210> 150
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
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<400> 150
aaagacctgt gcaaaatgtg gcactggatg tgcaaaccga aa 42

<210> 151
<211> 42
<212> DNA
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<220>
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<400> 151
tggtaccgt gctacgaatt ccacttctgg tgctacgacc tg 42

<210> 152
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
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42

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<400> 251

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<210> 252

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<210> 253

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

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<210> 254

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<212> DNA

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<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 254

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<210> 255

<211> 57

<212> DNA

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 255

aaacgtctgc tggaacagtt catgaacgac ctggctgaac tggtttccgg tcactcc 57

<210> 256

<211> 60

<212> DNA

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 256

gacacccgtg acgctctgtt ccaggaattc tacgaattcg ttcgttcccg tctggttatc 60

<210> 257

<211> 60

<212> DNA

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 257

cgtatgtccg ctgctccgcg tccgctgacc taccgtgaca tcatggacca gtactggcac 60

<210> 258

<211> 60

<212> DNA

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<400> 258

aacgacaaag ctcaattctt cgaaatgttc atgttcgacg ttcacaactt cgttgaatcc 60

<210> 259

<211> 60

<212> DNA

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<400> 259

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<210> 260

<211> 54

<212> DNA

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<400> 260
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<210> 261
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<400> 261
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<210> 262
<211> 60
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<400> 262
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<210> 263
<211> 60
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<400> 263
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<210> 264
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<220>
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<400> 264
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<210> 265
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<400> 265
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<210> 266
<211> 54
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<400> 266
cgtgctaccc tgctgaaaga cttctggcag ctggttgaag gttacgggtga caac 54

<210> 267
<211> 48
<212> DNA
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<220>
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<400> 267
gaagaactgc tgcgtgaatt ctaccgtttc gtttccgctt tcgactac 48

<210> 268
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<400> 268
ggtctgctgg acgaattctc ccacttcacg gctgaacagt tctaccagat gccgggtggt 60

<210> 269
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<210> 270
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<400> 270

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<210> 271
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<400> 271
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<210> 272
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<400> 272
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<210> 273
<211> 60
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<220>
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<400> 273
gaattcttcc actggctgca caaccaccgt tccgaagtta accactggct ggacatgaac 60

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<211> 57
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<400> 274
gaagctcttt ttcaaaattt ttttcgtgat gttcttactc tttctgaacg tgaatat 57

<210> 275
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<210> 276
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<210> 277
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<400> 277
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<210> 278
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<220>

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<400> 278
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<210> 279
<211> 45
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<223> Nucleotide sequence encoding Myostatin Binding Peptide

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<210> 280
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<212> DNA
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<220>

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<400> 280
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actcgttggc catggatgtg tccaccgtat 150

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<211> 129
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<400> 281
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tcttctggtt ccggttccgc tactggttgg taccctgtgt acgaagggtca cttttggtgt 120
tatgatctg 129

<210> 282
<211> 150
<212> DNA
<213> Artificial Sequence

<220>
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<400> 282
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ggtggttccg gttccactgc ttcttctggt tccggttctg caactgggtca caccctgtgc 120
ccgtggtttg caccgctgtg tgtagagtgg 150

<210> 283
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atcgaccggg attggtggtg taaattttgg 150

<210> 284
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 gggttactggc cgtggtcttg taaatggggt 150

<210> 287
 <211> 150
 <212> DNA
 <213> Artificial Sequence

<220>
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<210> 288
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<400> 288

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<400> 289

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actcgttggc catggatgtg tccgccgtat 150

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<212> DNA

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<400> 290

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<210> 291

<211> 102

<212> DNA

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<400> 291

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aaaaaacact gccagatctg gacttggatg tgcgctccga aa 102

<210> 292

<211> 37

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 292

gagagagagc atatgaatga gaacagtgag caaaaag

37

<210> 293

<211> 34

<212> DNA

<213> Artificial Sequence

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 293

agagagggat ccattatgag cacccacagc ggtc

34

<210> 294

<211> 25

<212> DNA

<213> Artificial Sequence

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 294

cggcgcaact atcggtatca agctg

25

<210> 295

<211> 26

<212> DNA

<213> Artificial Sequence

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 295

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26

<210> 296

<211> 227

<212> PRT

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<220>

<223> Myostatin Binding Peptide

<400> 296

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Lys | Thr | His | Thr | Cys | Pro | Pro | Cys | Pro | Ala | Pro | Glu | Leu | Leu | Gly |
| 1 | | | | 5 | | | | 10 | | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Pro | Ser | Val | Phe | Leu | Phe | Pro | Pro | Lys | Pro | Lys | Asp | Thr | Leu | Met |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Ser | Arg | Thr | Pro | Glu | Val | Thr | Cys | Val | Val | Val | Asp | Val | Ser | His |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|

35 40 45
 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 50 55 60
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 65 70 75 80
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 85 90 95
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
 100 105 110
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 115 120 125
 Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
 130 135 140
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 145 150 155 160
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 165 170 175
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 180 185 190
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 195 200 205
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 210 215 220
 Pro Gly Lys
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<210> 297

<211> 67

<212> DNA

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<220>

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ggggaca 67

<210> 298
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<400> 298
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<210> 299
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<400> 299
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<210> 300
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<210> 302
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 <212> DNA
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<400> 302
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<210> 303
 <211> 22
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<220>
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<400> 303

Met Phe Cys Gly Gly Gly Gly Lys Asp Lys Cys Lys Met Trp His
 1 5 10 15

Trp Met Cys Lys Pro Pro
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<210> 304
 <211> 740
 <212> DNA
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 acatgcgtgg tgggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg 180
 gacggcgtgg aggtgcataa tgccaagaca aagcccgagg aggagcagta caacagcacg 240

taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtag 300
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<210> 305
<211> 20
<212> PRT
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<400> 305

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1 5 10 15

Gln Arg Glu Gly
20

<210> 306
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 306

Tyr Pro Glu Gln Gly Leu Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Thr Leu Ala
20

<210> 307
<211> 20
<212> PRT
<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 307

Gly Leu Asn Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
 1 5 10 15

Gln Asp Ser Asn
 20

<210> 308

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 308

Met Ile Thr Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
 1 5 10 15

Gln Pro Ser Gly
 20

<210> 309

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 309

Ala Gly Ala Gln Glu His Cys Thr Arg Trp Pro Trp Met Cys Ala Pro
 1 5 10 15

Asn Asp Trp Ile
 20

<210> 310

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 310

Gly Val Asn Gln Gly Gln Cys Thr Arg Trp Arg Trp Met Cys Pro Pro
 1 5 10 15

Asn Gly Trp Glu
20

<210> 311
<211> 20
<212> PRT
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<220>
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<400> 311

Leu Ala Asp His Gly Gln Cys Ile Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Glu Gly Trp Glu
20

<210> 312
<211> 20
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<220>
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<400> 312

Ile Leu Glu Gln Ala Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Gly Gly
20

<210> 313
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<400> 313

Thr Gln Thr His Ala Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Trp Glu Gly
20

<210> 314

<211> 20
<212> PRT
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<220>
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<400> 314

Val Val Thr Gln Gly His Cys Thr Leu Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Trp Arg
20

<210> 315
<211> 20
<212> PRT
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<220>
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<400> 315

Ile Tyr Pro His Asp Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Pro Tyr Pro
20

<210> 316
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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<400> 316

Ser Tyr Trp Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Trp Arg Gly
20

<210> 317
<211> 20
<212> PRT
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<220>
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<400> 317

Met Trp Gln Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Gly
20

<210> 318

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 318

Glu Phe Thr Gln Trp His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Ser Gln
20

<210> 319

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 319

Leu Asp Asp Gln Trp Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Phe Ser
20

<210> 320

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 320

Tyr Gln Thr Gln Gly Leu Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Ser Gln Arg

20

<210> 321
 <211> 20
 <212> PRT
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<220>
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<400> 321

Glu Ser Asn Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
 1 5 10 15

Gln Gly Gly Trp
 20

<210> 322
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Myostatin Binding Peptide

<400> 322

Trp Thr Asp Arg Gly Pro Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
 1 5 10 15

Gln Ala Asn Gly
 20

<210> 323
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 323

Val Gly Thr Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
 1 5 10 15

Tyr Glu Thr Gly
 20

<210> 324
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<400> 324

Pro Tyr Glu Gln Gly Lys Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Tyr Glu Val Glu
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<210> 325

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 325

Ser Glu Tyr Gln Gly Leu Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Lys
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<210> 326

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

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<400> 326

Thr Phe Ser Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Gly
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<210> 327

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 327

Pro Gly Ala His Asp His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro

1 5 10 15

Gln Ser Arg Tyr
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<210> 328
<211> 20
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Val Ala Glu Glu Trp His Cys Arg Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Asp Trp Arg
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<211> 20
<212> PRT
<213> Artificial Sequence

<220>
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Val Gly Thr Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Pro Ala Gly
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<210> 330
<211> 20
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<400> 330

Glu Glu Asp Gln Ala His Cys Arg Ser Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Val
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<400> 331

Ala Asp Thr Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln His Trp Phe
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<400> 332

Ser Gly Pro Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Ala Pro
1 5 10 15

Gln Gly Trp Phe
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<400> 333

Thr Leu Val Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Trp Val
20

<210> 334
<211> 20
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Gly Met Ala His Gly Lys Cys Thr Arg Trp Ala Trp Met Cys Pro Pro
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Gln Ser Trp Lys
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<210> 335

<211> 20

<212> PRT

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<400> 335

Glu Leu Tyr His Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
 1 5 10 15

Gln Ser Trp Ala
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<210> 336

<211> 20

<212> PRT

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<400> 336

Val Ala Asp His Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
 1 5 10 15

Gln Gly Trp Gly
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<210> 337

<211> 20

<212> PRT

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<400> 337

Pro Glu Ser Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
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Gln Gly Trp Gly
20

<210> 338
<211> 20
<212> PRT
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<220>
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<400> 338

Ile Pro Ala His Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Trp Arg
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<210> 339
<211> 20
<212> PRT
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<220>
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<400> 339

Phe Thr Val His Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Tyr Gly Trp Val
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<210> 340
<211> 20
<212> PRT
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<400> 340

Pro Asp Phe Pro Gly His Cys Thr Arg Trp Arg Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Glu
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<210> 341
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<400> 341

Gln Leu Trp Gln Gly Pro Cys Thr Gln Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Lys Gly Arg Tyr
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<400> 342

His Ala Asn Asp Gly His Cys Thr Arg Trp Gln Trp Met Cys Pro Pro
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Gln Trp Gly Gly
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<210> 343

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<400> 343

Glu Thr Asp His Gly Leu Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Tyr Gly Ala Arg
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<210> 344

<211> 20

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Gly Thr Trp Gln Gly Leu Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
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Gln Gly Trp Gln
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<210> 345

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<400> 345

Val Ala Thr Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Gly Trp Gly
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<400> 346

Val Ala Thr Gln Gly Gln Cys Thr Arg Trp Pro Trp Met Cys Pro Pro
1 5 10 15

Gln Arg Trp Gly
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<210> 347

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<400> 347

Gln Arg Glu Trp Tyr Pro Cys Tyr Gly Gly His Leu Trp Cys Tyr Asp
1 5 10 15

Leu His Lys Ala
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<210> 348
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<212> PRT
<213> Artificial Sequence

<220>
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<400> 348

Ile Ser Ala Trp Tyr Ser Cys Tyr Ala Gly His Phe Trp Cys Trp Asp
1 5 10 15

Leu Lys Gln Lys
20

<210> 349
<211> 20
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<400> 349

Trp Thr Gly Trp Tyr Gln Cys Tyr Gly Gly His Leu Trp Cys Tyr Asp
1 5 10 15

Leu Arg Arg Lys
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<210> 350
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<400> 350

Lys Thr Phe Trp Tyr Pro Cys Tyr Asp Gly His Phe Trp Cys Tyr Asn
1 5 10 15

Leu Lys Ser Ser
20

<210> 351
<211> 20
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<400> 351

Glu Ser Arg Trp Tyr Pro Cys Tyr Glu Gly His Leu Trp Cys Phe Asp
1 5 10 15

Leu Thr Glu Thr
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<212> PRT

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<222> (2)..(3)

<223> Xaa is selected from a neutral hydrophobic, neutral polar, or basic amino acid

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<222> (5)..(5)

<223> Xaa is selected from a neutral hydrophobic, neutral polar, or basic amino acid

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<210> 353

<211> 10

<212> PRT

<213> Artificial Sequence

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<222> (2)..(2)

<223> Xaa is selected from any one of the amino acids T, I, or R.

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> Xaa is selected from any one of R, S, Q.

<220>

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<222> (5)..(5)

<223> Xaa is selected from any one of P, R, and Q.

<400> 353

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<212> PRT

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<223> Xaa is absent or any amino acid

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<222> (2)..(3)

<223> Xaa is absent or a neutral hydrophobic, neutral polar, or acidic amino acid

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<222> (4)..(4)

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<223> Xaa is any amino acid

<400> 354

<223> Xaa is selected from any one of P, R and Q

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 <222> (17)..(20)
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 1 5 10 15

Xaa Xaa Xaa Xaa
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 <223> Xaa is G or H

<400> 356

Trp Tyr Xaa Xaa Tyr Xaa Gly
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 <211> 22
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 357

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
 1 5 10 15

Pro Met Ser Lys Ala Gly
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<210> 358
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 358

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Met Ser Lys Ala Arg
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<210> 359
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
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<400> 359

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Asp Ile Val
1 5 10 15

Pro Met Ser Lys Pro Ser
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<210> 360
<211> 22
<212> PRT
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<400> 360

Gly Met Glu Met Leu Glu Ser Leu Phe Glu Leu Leu Gln Glu Ile Val
1 5 10 15

Pro Met Ser Lys Ala Pro
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<400> 361

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Asp Ile Val
1 5 10 15

Pro Ile Ser Asn Pro Pro
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<210> 362

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<400> 362

Arg Ile Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Gln Glu Ile Val
1 5 10 15

Pro Ile Ser Lys Ala Glu
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<211> 22

<212> PRT

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<400> 363

Arg Met Glu Met Leu Gln Ser Leu Leu Glu Leu Leu Lys Asp Ile Val
1 5 10 15

Pro Met Ser Asn Ala Arg
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1 5 10 15

Pro Thr Ser Asn Gly Thr
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<210> 365
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<400> 365

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1 5 10 15

Pro Met Ser Lys Ala Gly
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<210> 366
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<400> 366

Arg Met Glu Met Leu Gly Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Met Ser Lys Ala Arg
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<210> 367
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<220>
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<400> 367

Gln Met Glu Leu Leu Asp Ser Leu Phe Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Lys Ser Gln Pro Ala
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<210> 368

<211> 22
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Arg Met Glu Met Leu Asp Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Met Ser Asn Ala Arg
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<400> 369

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu His Glu Ile Val
1 5 10 15

Pro Met Ser Gln Ala Gly
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<210> 370
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<400> 370

Gln Met Glu Met Leu Glu Ser Leu Leu Gln Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Met Ser Lys Ala Ser
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<210> 371
<211> 22
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<220>
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<400> 371

Arg Met Glu Met Leu Asp Ser Leu Leu Glu Leu Leu Lys Asp Met Val
1 5 10 15

Pro Met Thr Thr Gly Ala
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<210> 372

<211> 22

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<400> 372

Arg Ile Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Asp Met Val
1 5 10 15

Pro Met Ala Asn Ala Ser
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<400> 373

Arg Met Glu Met Leu Glu Ser Leu Leu Gln Leu Leu Asn Glu Ile Val
1 5 10 15

Pro Met Ser Arg Ala Arg
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<211> 22

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<400> 374

Arg Met Glu Met Leu Glu Ser Leu Phe Asp Leu Leu Lys Glu Leu Val
1 5 10 15

Pro Met Ser Lys Gly Val

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<210> 375
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<400> 375

Arg Ile Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Asp Ile Val
1 5 10 15

Pro Ile Gln Lys Ala Arg
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<210> 376
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<400> 376

Arg Met Glu Leu Leu Glu Ser Leu Phe Glu Leu Leu Lys Asp Met Val
1 5 10 15

Pro Met Ser Asp Ser Ser
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<210> 377
<211> 22
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<400> 377

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Val Leu Gln Glu Ile Val
1 5 10 15

Pro Arg Ala Lys Gly Ala
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<400> 378

Arg Met Glu Met Leu Asp Ser Leu Leu Gln Leu Leu Asn Glu Ile Val
1 5 10 15

Pro Met Ser His Ala Arg
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<210> 379

<211> 22

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<400> 379

Arg Met Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Lys Asp Ile Val
1 5 10 15

Pro Met Ser Asn Ala Gly
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<210> 380

<211> 22

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<400> 380

Arg Met Glu Met Leu Gln Ser Leu Phe Glu Leu Leu Lys Gly Met Val
1 5 10 15

Pro Ile Ser Lys Ala Gly
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<210> 381

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<220>

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<400> 381

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1 5 10 .15

Pro Asn Ser Thr Ala Ala
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<220>
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<400> 382

Arg Met Glu Met Leu Gln Ser Leu Leu Glu Leu Leu Lys Glu Ile Val
1 5 10 15

Pro Ile Ser Lys Ala Gly
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| <210> | 383 |
| <211> | 22 |
| <212> | PRT |
| <213> | Artificial Sequence |

<220>
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<400> 383

Arg Ile Glu Met Leu Asp Ser Leu Leu Glu Leu Leu Asn Glu Leu Val
1 5 10 15

Pro Met Ser Lys Ala Arg
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<210> 384
<211> 22
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<220>
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<400> . 384

Gln Val Glu Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln Gly
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<210> 385
<211> 22
<212> PRT
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<220>
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<400> 385

Arg Met Glu Leu Leu Glu Ser Leu Phe Glu Leu Leu Lys Glu Met Val
1 5 10 15

Pro Arg Ser Lys Ala Val
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<210> 386
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<220>
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<400> 386

Gln Ala Val Ser Leu Gln His Leu Leu Met Trp Leu Asp Gln Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln His
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<210> 387
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<220>
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<400> 387

Asp Glu Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln Leu
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<210> 388
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<220>
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<400> 388

Pro Val Ala Ser Leu Gln Gln Leu Leu Ile Trp Leu Asp Gln Lys Leu
1 5 10 15

Ala Gln Gly Pro His Ala
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<210> 389

<211> 22

<212> PRT

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<220>

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<400> 389

Glu Val Asp Glu Leu Gln Gln Leu Leu Asn Trp Leu Asp His Lys Leu
1 5 10 15

Ala Ser Gly Pro Leu Gln
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<210> 390

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Asp Val Glu Ser Leu Glu Gln Leu Leu Met Trp Leu Asp His Gln Leu
1 5 10 15

Ala Ser Gly Pro His Gly
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<210> 391

<211> 22

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Gln Val Asp Ser Leu Gln Gln Val Leu Leu Trp Leu Glu His Lys Leu
1 5 10 15

Ala Leu Gly Pro Gln Val
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<210> 392
<211> 22
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<220>
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<400> 392

Gly Asp Glu Ser Leu Gln His Leu Leu Met Trp Leu Glu Gln Lys Leu
1 5 10 15

Ala Leu Gly Pro His Gly
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<210> 393
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<220>
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<400> 393

Gln Ile Glu Met Leu Glu Ser Leu Leu Asp Leu Leu Arg Asp Met Val
1 5 10 15

Pro Met Ser Asn Ala Phe
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<210> 394
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<220>
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<400> 394

Glu Val Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln Ala
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<210> 395
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<220>

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<400> 395

Glu Asp Glu Ser Leu Gln Gln Leu Leu Ile Tyr Leu Asp Lys Met Leu
1 5 10 15

Ser Ser Gly Pro Gln Val
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<210> 396

<211> 22

<212> PRT

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<220>

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<400> 396

Ala Met Asp Gln Leu His Gln Leu Leu Ile Trp Leu Asp His Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln Ala
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<210> 397

<211> 22

<212> PRT

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<220>

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<400> 397

Arg Ile Glu Met Leu Glu Ser Leu Leu Glu Leu Leu Asp Glu Ile Ala
1 5 10 15

Leu Ile Pro Lys Ala Trp
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<210> 398

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<400> 398

Glu Val Val Ser Leu Gln His Leu Leu Met Trp Leu Glu His Lys Leu
 1 5 10 15

Ala Ser Gly Pro Asp Gly
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<210> 399
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<400> 399

Gly Gly Glu Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Gln Leu
 1 5 10 15

Ala Ser Gly Pro Gln Arg
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<210> 400
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Val Ser Gly Pro His Asp
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<210> 401
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<400> 401

Asn Val Glu Ser Leu Glu His Leu Met Met Trp Leu Glu Arg Leu Leu
 1 5 10 15

Ala Ser Gly Pro Tyr Ala
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<210> 402
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<400> 402

Gln Val Asp Ser Leu Gln Gln Leu Leu Ile Trp Leu Asp His Gln Leu
1 5 10 15

Ala Ser Gly Pro Lys Arg
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<210> 403
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1 5 10 15

Ala Gln Gly Pro Gln Gly
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Ala Ser Gly Pro His Ala
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<210> 405
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<400> 405

Glu Val Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Gln Leu
1 5 10 15

Ala Ser Gly Pro Gln Lys
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<210> 406

<211> 22

<212> PRT

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Gly Val Glu Gln Leu Pro Gln Leu Leu Met Trp Leu Glu Gln Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln Arg
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<210> 407

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Gly Glu Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Gln Leu
1 5 10 15

Ala Ala Gly Pro Gln Val
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<210> 408

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<220>

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<400> 408

Ala Asp Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Arg Lys Leu
1 5 10 15

Ala Ser Gly Pro His Val
20

<210> 409
<211> 22
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Leu Gly Asp Asn Leu Val
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Leu Gly Asp Lys Gln Ala
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<212> PRT
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Asp Gly Arg Ala Thr Leu Leu Thr Glu Phe Trp Gln Leu Val Gln Gly
1 5 10 15

Leu Gly Gln Lys Glu Ala
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<400> 413

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1 5 10 15

Leu Gly Glu Lys Val Val
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<400> 414

Gly Ser Arg Asp Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Val Gly
1 5 10 15

Leu Gly Asp Met Gln Thr
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<210> 415
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<400> 415

Asp Ala Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Asp Ala
1 5 10 15

Tyr Gly Asp Arg Met Val
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<210> 416
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Asn Asp Arg Ala Gln Leu Leu Arg Asp Phe Trp Gln Leu Val Asp Gly
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Leu Gly Val Lys Ser Trp
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<220>
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<400> 417

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1 5 10 15

Leu Gly Ala Asn Gln Gly
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<210> 418
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<220>
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<400> 418

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1 5 10 15

Gln Gly Asp Lys Leu Ser
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<210> 419
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<400> 419

Gln Glu Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Ala Gly
1 5 10 15

Leu Gly Gln Asn Met Arg
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<210> 420
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<220>
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<400> 420

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1 5 10 15

Leu Gly Glu Tyr Arg Trp
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<210> 421
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<400> 421

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1 5 10 15

Gln Arg Glu Met Gln Trp
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<400> 422

Gly Glu Arg Ala Thr Leu Leu Asn Asp Phe Trp Gln Leu Val Asp Gly
1 5 10 15

Gln Gly Asp Asn Thr Gly
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<400> 423

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Trp Gly Asp Asn Val Ala
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<400> 424

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Gln Gly Ala Asn Leu Val
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1 5 10 15

Tyr Gly Asp Lys Leu Val
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<400> 426

Gly Met Arg Ala Thr Leu Leu Gln Glu Phe Trp Gln Leu Val Gly Gly
1 5 10 15

Gln Gly Asp Asn Trp Met
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<210> 427
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<400> 427

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Trp Ala Glu Asp Arg Gly
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<400> 428

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Trp Gly Asp Asn Phe Gly
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<400> 429

Val Gly Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Glu Gly
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Leu Val Gly Gln Ser Arg
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<400> 430

Glu Ile Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Val Asp Glu
1 5 10 15

Trp Arg Glu Gln Pro Asn
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<210> 431
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<400> 431

Gln Leu Arg Ala Thr Leu Leu Lys Glu Phe Leu Gln Leu Val His Gly
1 5 10 15

Leu Gly Glu Thr Asp Ser
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<210> 432
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<220>
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<400> 432

Thr Gln Arg Ala Thr Leu Leu Lys Glu Phe Trp Gln Leu Ile Glu Gly
1 5 10 15

Leu Gly Gly Lys His Val
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<400> 433

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Leu Arg Glu Gln Gly Val
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<400> 434

Gln Ser Arg Val Thr Leu Leu Arg Glu Phe Trp Gln Leu Val Glu Ser
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Tyr Arg Pro Ile Val Asn
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<210> 435

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<220>

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<400> 435

Leu Ser Arg Ala Thr Leu Leu Asn Glu Phe Trp Gln Phe Val Asp Gly
1 5 10 15

Gln Arg Asp Lys Arg Met

20

<210> 436
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<400> 436

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Leu Ser Gln Lys Pro Gly
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<210> 437
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<220>
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<400> 437

Gln Glu Arg Ala Thr Leu Leu Lys Glu Phe Trp Arg Met Val Glu Gly
1 5 10 15

Leu Gly Lys Asn Arg Gly
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<210> 438
<211> 22
<212> PRT
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<220>
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<400> 438

Asn Glu Arg Ala Thr Leu Leu Arg Glu Phe Trp Gln Leu Val Gly Gly
1 5 10 15

Tyr Gly Val Asn Gln Arg
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<210> 439
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<220>

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<400> 439

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1 5 10 15

Gly Leu Arg Gln Tyr Ser
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<210> 440

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 440

Thr Gln Arg Asp Met Ser Met Leu Asp Gly Leu Leu Glu Val Leu Asp
1 5 10 15

Gln Leu Arg Gln Gln Arg
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<210> 441

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 441

Thr Ser Arg Asp Met Ser Leu Leu Trp Glu Leu Leu Glu Glu Leu Asp
1 5 10 15

Arg Leu Gly His Gln Arg
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<210> 442

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 442

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1 5 10 15

Ser Leu Gly His Gln Ile
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<220>
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<400> 443

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1 5 10 15

Gly Leu Arg Gln Gln Val
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<210> 444
<211> 22
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<220>
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<400> 444

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1 5 10 15

Arg Leu Gly Pro Gln Leu
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<220>
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Arg Leu Gly Gln Gln Arg
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<210> 446
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<212> PRT
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<220>
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<400> 446

Trp Tyr Arg Asp Met Ser Met Leu Gly Leu Leu Glu Val Leu Asp
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Arg Leu Gly Gln Gln Arg
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<210> 447
<211> 22
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<220>
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<400> 447

Thr Gln Asn Ser Arg Gln Met Leu Leu Ser Asp Phe Met Met Leu Val
1 5 10 15

Gly Ser Met Ile Gln Gly
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<210> 448
<211> 22
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<220>
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<400> 448

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1 5 10 15

Gly Ser Ile Met His Gly
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<210> 449
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<220>
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<400> 449

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1 5 10 15

Gly Thr Met Ile Gln Gly
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<210> 450

<211> 22

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<220>

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<400> 450

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Gly Asn Met Ser His Gln
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<210> 451

<211> 22

<212> PRT

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<220>

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<400> 451

Gln Asp Thr Ser Arg His Met Leu Leu Arg Glu Phe Met Met Leu Val
1 5 10 15

Gly Glu Met Ile Gln Gly
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<210> 452

<211> 22

<212> PRT

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<220>

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<400> 452

Asp Gln Asn Ser Arg Gln Met Leu Leu Ser Asp Leu Met Ile Leu Val
1 5 10 15

Gly Ser Met Ile Gln Gly
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<210> 453
<211> 22
<212> PRT
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<220>
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<400> 453

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1 5 10 15

Trp Leu Asp Ile Asn Val
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<210> 454
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<212> PRT
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<220>
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<400> 454

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Trp Leu Val Met Asp Val
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<210> 460
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<210> 461
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<210> 463
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ccagct 66

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<210> 470

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<210> 473
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gcttct 66

<210> 474
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<213> Artificial Sequence

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<210> 485

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<210> 486
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<210> 487
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<210> 488
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<210> 490

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<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 490

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tcttgg 66

<210> 491

<211> 66

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 491

ggtgttcgtg aaactcttct ttatgaactt tggatcttct ttaaagggtct tgggtgta 60

caaggt 66

<210> 492

<211> 66

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 492

caagctcgtg ctactcttct taaagaattt tgtcaacttg ttggttggtca aggtgata 60

ctttct 66

<210> 493

<211> 66

<212> DNA

<213> Artificial Sequence

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<400> 493

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. atgcgt 66

<210> 494
<211> 66
<212> DNA
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<220>
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<400> 494
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cgttgg 66

<210> 495
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
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<400> 495
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caatgg 66

<210> 496
<211> 66
<212> DNA
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<220>
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<400> 496
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actggt 66

<210> 497
<211> 66
<212> DNA
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<220>
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gttgct 66

<210> 498
<211> 66

<212> DNA
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 <400> 498
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 cttgtt 66
 <210> 499
 <211> 66
 <212> DNA
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 <223> Nucleotide sequence encoding Myostatin Binding Peptide
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 cttgtt 66
 <210> 500
 <211> 66
 <212> DNA
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 <223> Nucleotide sequence encoding Myostatin Binding Peptide
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 tgggatg 66
 <210> 501
 <211> 66
 <212> DNA
 <213> Artificial Sequence
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 <223> Nucleotide sequence encoding Myostatin Binding Peptide
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 cgtgggt 66
 <210> 502
 <211> 66
 <212> DNA
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<400> 502
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 tttggt 66

<210> 503
 <211> 66
 <212> DNA
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<220>
 <223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 503
 gttggtcgtg ctactcttct taaagaattt tggcaacttg ttgaaggtct tgttggtcaa 60
 tctcgt 66

<210> 504
 <211> 62
 <212> PRT
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<220>
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<220>
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 <222> (62)..(62)
 <223> Xaa = Fc

<400> 504

Met Gly Ala Gln Trp Tyr Pro Cys Tyr Glu Gly His Phe Trp Cys Tyr
 1 5 10 15

Asp Leu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser
 20 25 30

Ser Gly Ser Gly Ser Ala Thr Gly Trp Tyr Pro Cys Tyr Glu Gly His
 35 40 45

Phe Trp Cys Tyr Asp Leu Leu Glu Gly Gly Gly Gly Xaa
 50 55 60

<210> 505
 <211> 129
 <212> DNA
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<220>
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<400> 505
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 tcttctgggt cgggttccgc tactgggtgg taccctgtgct acgaagggtca cttttgggtgt 120
 tatgatctg 129

<210> 506
 <211> 60
 <212> PRT
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<220>
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 <222> (1)..(1)
 <223> Xaa = Fc

<400> 506

Xaa Gly Gly Gly Gly Gly Ala Gln Trp Tyr Pro Cys Tyr Glu Gly His
 1 5 10 15

Phe Trp Cys Tyr Asp Leu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly
 20 25 30

Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Trp Tyr Pro Cys
 35 40 45

Tyr Glu Gly His Phe Trp Cys Tyr Asp Leu Leu Glu
 50 55 60

<210> 507
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 <212> DNA
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<220>
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<400> 507
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 tcttctgggt cgggttccgc tactgggtgg taccctgtgct acgaagggtca cttttgggtgt 120
 tatgatctg 129

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<222> (62)..(62)

<223> Xaa = Fc

<400> 508

Met Gly Ala Gln Ile Phe Gly Cys Lys Trp Trp Asp Val Gln Cys Tyr
 1 5 10 15

Gln Phe Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser
 20 25 30

Ser Gly Ser Gly Ser Ala Thr Gly Ile Phe Gly Cys Lys Trp Trp Asp
 35 40 45

Val Gln Cys Tyr Gln Phe Leu Glu Gly Gly Gly Gly Gly Xaa
 50 55 60

<210> 509

<211> 129

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 509

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tcttctggtt ccggttcgc tactggtatc ttcggttgca agtggtggga tgtacagtgt 120

tatcagttt 129

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<221> MISC_FEATURE

<222> (1)..(1)

<223> Xaa = Fc

<400> 510

Xaa Gly Gly Gly Gly Gly Ala Gln Ile Phe Gly Cys Lys Trp Trp Asp
 1 5 10 15

Val Gln Cys Tyr Gln Phe Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly
 20 25 30

Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Ile Phe Gly Cys
 35 40 45

Lys Trp Trp Asp Val Gln Cys Tyr Gln Phe Leu Glu
 50 55 60

<210> 511
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<400> 511
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 tatcagttt 129

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Met Gly Ala Gln Ile Phe Gly Cys Lys Trp Trp Asp Val Asp Cys Tyr
 1 5 10 15

Gln Phe Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser
 20 25 30

Ser Gly Ser Gly Ser Ala Thr Gly Ile Phe Gly Cys Lys Trp Trp Asp
 35 40 45

Val Asp Cys Tyr Gln Phe Leu Glu Gly Gly Gly Gly Gly Xaa
 50 55 60

<210> 513
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 tcttctgggtt ccggttccgc tactgggtatc ttcggttgca aatggtggga cgttgattgt 120
 tatcagttt 129

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 1 5 10 15

Val Asp Cys Tyr Gln Phe Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly
 20 25 30

Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Ile Phe Gly Cys
 35 40 45

Lys Trp Trp Asp Val Asp Cys Tyr Gln Phe Leu Glu
 50 55 60

<210> 515
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tatcagttt

129

<210> 516

<211> 66

<212> DNA

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<400> 516

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66

<210> 517

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<212> DNA

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<400> 517

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gctggt

66

<210> 518

<211> 66

<212> DNA

<213> Artificial Sequence

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 518

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cagcac

66

<210> 519

<211> 66

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<400> 519

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cagctg

66

<210> 520

<211> 66
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<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 520

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cacgct 66

<210> 521
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<400> 521

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ctgcag 66

<210> 522
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<400> 522

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cacggt 66

<210> 523
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<400> 523

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caggtt 66

<210> 524
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<400> 524

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cacggt 66

<210> 525

<211> 66

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<400> 525

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gcttttc 66

<210> 526

<211> 66

<212> DNA

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<400> 526

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caggct 66

<210> 527

<211> 66

<212> DNA

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<400> 527

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caggtt 66

<210> 528

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<212> DNA

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<400> 528

gctatggacc agctgcacca gctgctgatc tggctggacc acaaactggc ttccggtccg 60

caggct

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<210> 529

<211> 66

<212> DNA

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<400> 529

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gcttgg

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gacggt

66

<210> 531

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cagcgt

66

<210> 532

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cacgac

66

<210> 533

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<400> 533

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<210> 535

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<212> DNA

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 535

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cagggt 66

<210> 536

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cacgct 66

<210> 537

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cagaaa 66

<210> 538
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cagcgt 66

<210> 539
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caggtt 66

<210> 540
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<400> 540
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cacgtt 66

<210> 541
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caggggt 66

<210> 542
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caggct 66

<210> 543
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ccgaac 66

<210> 544
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gactcc 66

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cacgtt 66

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gttaac 66

<210> 548

<211> 66

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cgtatg 66

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ccgggt 66

<210> 550

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cgtggt 66

<210> 551
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<400> 551
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cagcgt 66

<210> 552
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<210> 555
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<400> 555

aaaaccttct ggtacccgtg ctacgacggt cacttctggt gctacaacct gaaatcctcc 60

<210> 556

<211> 60

<212> DNA

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gaatcccgtt ggtacccgtg ctacgaaggt cacctgtggt gcttcgacct gaccgaaacc 60

<210> 557

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<212> DNA

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 557

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aatgtt 66

<210> 558

<211> 66

<212> DNA

<213> Artificial Sequence

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 558

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gatgtt 66

<210> 559

<211> 66

<212> DNA

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<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

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tattct 66

<210> 560
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<400> 560
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caacgt 66

<210> 561
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<400> 561
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cagcgt 66

<210> 562
<211> 66
<212> DNA
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<400> 562
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caaatt 66

<210> 563
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<400> 563
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caagtt 66

<210> 564
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<212> DNA
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<400> 564

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 caactt 66

<210> 565

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<212> DNA

<213> Artificial Sequence

<220>

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<400> 565

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 caacgt 66

<210> 566

<211> 66

<212> DNA

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<400> 566

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<210> 567

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<400> 567

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 caaggt 66

<210> 568

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<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 568

atgcaaacct ctcgtcatat tcttctttct gaatttatga tgcttggttg ttctattatg 60

catgggt 66

<210> 569
 <211> 66
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 569
 caccgacaact cccgtcagat gctgctgtcc gacctgctgc acctgggttg taccatgatc 60
 cagggt 66

<210> 570
 <211> 66
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 570
 atggaaaact cccgtcagaa cctgctgcgt gaactgatca tgctgggttg taacatgtcc 60
 caccag 66

<210> 571
 <211> 66
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 571
 caggacacct cccgtcacat gctgctgcgt gaattcatga tgctgggttg tgaaatgatc 60
 cagggt 66

<210> 572
 <211> 66
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 572
 gaccagaact cccgtcagat gctgctgtcc gacctgatga tcctgggttg ttccatgatc 60
 cagggt 66

<210> 573

<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 573
gttgctcttc atgggtcaatg tactcgttgg ccatggatgt gtccaccaca acgtgaaggt 60

<210> 574
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 574
tatccagaac aaggctcttg tactcgttgg ccatggatgt gtccaccaca aactcttgct 60

<210> 575
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 575
ggtctgaacc agggtcactg caccggttg ccgtggatgt gcccgccgca ggactccaac 60

<210> 576
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 576
atgattactc aagggtcaatg tactcgttgg ccatggatgt gtccaccaca accatctggt 60

<210> 577
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 577
gctggtgctc aggaacactg caccggttg ccgtggatgt gcgctccgaa cgactggatc 60

<210> 578
<211> 60

<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 578
gggtgtaacc aggtcagtg caccggttg cggtggatgt gcccgccgaa cggttgggaa 60

<210> 579
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 579
ctggctgacc acgtcagtg catccgttg ccgtggatgt gcccgccgga aggttgggaa 60

<210> 580
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 580
atcctggaac aggtcagtg caccggttg ccgtggatgt gcccgccgca gcgtggtggt 60

<210> 581
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 581
actcaaactc atgtcaatg tactcgttg ccatggatgt gtccaccaca atgggaaggt 60

<210> 582
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 582
gttggtactc aaggtcattg tactcttttg ccatggatgt gtccaccaca acgttggcgt 60

<210> 583
<211> 60
<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 583
atttatccac atgatcaatg tactcgttgg ccatggatgt gtccaccaca accatatcca 60

<210> 584
<211> 60
<212> DNA
<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 584
tcttattggc aagggtcaatg tactcgttgg ccatggatgt gtccaccaca atggcggtgg 60

<210> 585
<211> 60
<212> DNA
<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 585
atgtggcaac aagggtcattg tactcgttgg ccatggatgt gtccaccaca aggttgggggt 60

<210> 586
<211> 60
<212> DNA
<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 586
gaattcaccc agtggcactg caccggttgg ccgtggatgt gcccgccgca gcgttcccag 60

<210> 587
<211> 60
<212> DNA
<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 587
ctggacgacc agtggcagtg caccggttgg ccgtggatgt gcccgccgca gggtttctcc 60

<210> 588
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 588
tatcaaactc aaggtctttg tactcgttgg ccatggatgt gtccaccaca atctcaacgt 60

<210> 589
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 589
gaatctaadc aaggtcaatg tactcgttgg ccatggatgt gtccaccaca aggtggttgg 60

<210> 590
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 590
tggaccgacc gtggtccgtg caccggttgg ccgtggatgt gcccgccgca ggctaaccgt 60

<210> 591
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 591
gttggtagcc agggtagtg caccggttgg ccgtggatgt gcccgccgta cgaaaccgtg 60

<210> 592
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 592
ccgtacgaac agggtagtg caccggttgg ccgtggatgt gcccgccgta cgaagttgaa 60

<210> 593
<211> 60
<212> DNA
<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 593

tccgaatacc agggctctgtg caccgcgttg ccgtggatgt gcccgccgca gggttgga 60

<210> 594

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 594

accttctccc agggctcactg caccgcgttg ccgtggatgt gcccgccgca gggttgggg 60

<210> 595

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 595

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<210> 596

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 596

gttgctgaag aatggcactg ccgtcggttg ccgtggatgt gcccgccgca ggactggcgt 60

<210> 597

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 597

gttggtaccc agggctcactg caccgcgttg ccgtggatgt gcccgccgca gccggctgg 60

<210> 598

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 598
gaagaagacc agggtcactg ccgttcctgg ccgtggatgt gcccgccgca gggttgggtt 60

<210> 599
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 599
gctgacaccc agggtcactg caccggttgg ccgtggatgt gcccgccgca gcactgggtc 60

<210> 600
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 600
tccggtccgc agggtcactg caccggttgg ccgtggatgt gcgctccgca gggttgggtc 60

<210> 601
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 601
accctgggtc agggtcactg caccggttgg ccgtggatgt gcccgccgca gcgttgggtt 60

<210> 602
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 602
ggatgggtc acggtaaag caccggttgg gcttggatgt gcccgccgca gtcctggaaa 60

<210> 603
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 603

gaactgtacc acggtcagtg caccggttgg ccgtggatgt gcccgccgca gtcctgggct 60

<210> 604

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 604

gttgctgacc acggtcactg caccggttgg ccgtggatgt gcccgccgca gggttggggt 60

<210> 605

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 605

ccggaatccc agggtcactg caccggttgg ccgtggatgt gcccgccgca gggttggggt 60

<210> 606

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 606

atcccggtc acggtcactg caccggttgg ccgtggatgt gcccgccgca gcgttggcgt 60

<210> 607

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 607

ttcacggtc acggtcactg caccggttgg ccgtggatgt gcccgccgta cggttggggt 60

<210> 608

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 608
ccagattttc caggtcattg tactcgttgg cgttgatgt gtcaccaca aggttgggaa 60

<210> 609
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 609
cagctgtggc aggggtccgtg caccagtg cgttgatgt gcccgccgaa aggtcggtac 60

<210> 610
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 610
cacgctaacg acggtcactg caccggttg cgttgatgt gcccgccgca gtggggtggt 60

<210> 611
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 611
gaaaccgacc acggtctgtg caccggttg cgttgatgt gcccgccgta cgtgctcgt 60

<210> 612
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 612
ggtacctggc agggctctgtg caccggttg cgttgatgt gcccgccgca ggttggcag 60

<210> 613
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 613

gttgctaccc agggtcagtg caccggttg ccgtggatgt gcccgccgca gggttggggt 60

<210> 614

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 614

gttgctaccc agggtcagtg caccggttg ccgtggatgt gcccgccgca gcgttggggt 60

<210> 615

<211> 74

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptibody

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> Xaa = Fc

<400> 615

Xaa Gly Gly Gly Gly Gly Ala Gln Leu Ala Asp His Gly Gln Cys Ile
1 5 10 15

Arg Trp Pro Trp Met Cys Pro Pro Glu Gly Trp Glu Leu Glu Gly Ser
20 25 30

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
35 40 45

Ser Ala Thr Gly Leu Ala Asp His Gly Gln Cys Ile Arg Trp Pro Trp
50 55 60

Met Cys Pro Pro Glu Gly Trp Glu Leu Glu
65 70

<210> 616

<211> 198

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 616

cttgctgac atgggtcaatg tattcggttg ccatggatgt gtccaccaga aggttgggaa 60

ctcgaggggtt ccggttccgc taccggcggc tctggctcca ctgcttcttc cggttccggt 120
 tctgtacttg gtctggctga ccacggtcag tgcattccgtt ggccgtggat gtgcccgcgc 180
 gaaggttggg aactggaa 198

<210> 617
 <211> 70
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Peptibody

<220>
 <221> MISC_FEATURE
 <222> (1)..(1)
 <223> Xaa = Fc

<400> 617

Xaa Gly Gly Gly Gly Gly Ala Gln Leu Ala Asp His Gly Gln Cys Ile
 1 5 10 15

Arg Trp Pro Trp Met Cys Pro Pro Glu Gly Trp Glu Gly Ser Gly Ser
 20 25 30

Ala Thr Gly Gly Ser Gly Gly Gly Ala Ser Ser Gly Ser Gly Ser Ala
 35 40 45

Thr Gly Leu Ala Asp His Gly Gln Cys Ile Arg Trp Pro Trp Met Cys
 50 55 60

Pro Pro Glu Gly Trp Glu
 65 70

<210> 618
 <211> 186
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 618
 cttgctgac atggtcaatg tattcgttgg ccatggatgt gtccaccaga aggttgggaa 60
 ggttccggtt ccgctaccgg cggctctggc ggtggcgctt cttccggttc cggttctgct 120
 actggtctgg ctgaccacgg tcagtgcac cgttggccgt ggatgtgtcc accagaaggt 180
 tgggaa 186

<210> 619
 <211> 74
 <212> PRT
 <213> Artificial Sequence

<220>
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<220>
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 <222> (1)..(1)
 <223> Xaa = Fc

<400> 619

Xaa Gly Gly Gly Gly Gly Ala Gln Ser Glu Tyr Gln Gly Leu Cys Thr
 1 5 10 15

Arg Trp Pro Trp Met Cys Pro Pro Gln Gly Trp Lys Leu Glu Gly Ser
 20 25 30

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 35 40 45

Ser Ala Thr Gly Ser Glu Tyr Gln Gly Leu Cys Thr Arg Trp Pro Trp
 50 55 60

Met Cys Pro Pro Gln Gly Trp Lys Leu Glu
 65 70

<210> 620
 <211> 198
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 620
 tctgaatatc aaggtctttg tactcgttgg ccatggatgt gtccaccaca aggttgga 60
 ctcgagggtt cgggttcgc taccggcggc tctggctcca ctgcttcttc cggttccggt 120
 tctgctactg gttctgagta tcaaggcctc tgtactcgct ggccatggat gtgtccacca 180
 caaggctgga agctggaa 198

<210> 621
 <211> 70
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Peptibody

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> Xaa = Fc

<400> 621

Xaa Gly Gly Gly Gly Gly Ala Gln Ser Glu Tyr Gln Gly Leu Cys Thr
1 5 10 15

Arg Trp Pro Trp Met Cys Pro Pro Gln Gly Trp Lys Gly Ser Gly Ser
20 25 30

Ala Thr Gly Gly Ser Gly Gly Gly Ala Ser Ser Gly Ser Gly Ser Ala
35 40 45

Thr Gly Ser Glu Tyr Gln Gly Leu Cys Thr Arg Trp Pro Trp Met Cys
50 55 60

Pro Pro Gln Gly Trp Lys
65 70

<210> 622

<211> 186

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 622

tctgaatatc aaggtctttg tactcgttgg ccatggatgt gtccaccaca aggttggaag 60
ggttccggtt ccgctaccgg cggctctggc ggtggcgctt cttccggttc cggttctgct 120
actggttctg agtatcaagg cctctgtact cgctggccat ggatgtgtcc accacaaggt 180
tggaag 186

<210> 623

<211> 74

<212> PRT

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<220>

<223> Peptibody

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> Xaa = Fc

<400> 623

Xaa Gly Gly Gly Gly Gly Ala Gln Thr Phe Ser Gln Gly His Cys Thr
 1 5 10 15

Arg Trp Pro Trp Met Cys Pro Pro Gln Gly Trp Gly Leu Glu Gly Ser
 20 25 30

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 35 40 45

Ser Ala Thr Gly Thr Phe Ser Gln Gly His Cys Thr Arg Trp Pro Trp
 50 55 60

Met Cys Pro Pro Gln Gly Trp Gly Leu Glu
 65 70

<210> 624

<211> 198

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 624

actttttctc aaggtcattg tactcgttgg ccatggatgt gtccaccaca aggttgggggt 60
 ctcgaggggtt ccggttccgc taccggcggc tctggctcca ctgcttcttc cggttccggt 120
 tctgctactg gtactttttc tcaaggccat tgtactcgct ggccatggat gtgtccacca 180
 caaggctggg gcctggaa 198

<210> 625

<211> 74

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptibody

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> Xaa = Fc

<400> 625

Xaa Gly Gly Gly Gly Gly Ala Gln Val Ala Asp His Gly His Cys Thr
 1 5 10 15

Arg Trp Pro Trp Met Cys Pro Pro Gln Gly Trp Gly Leu Glu Gly Ser
 20 25 30

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 35 40 45

Ser Ala Thr Gly Val Ala Asp His Gly His Cys Thr Arg Trp Pro Trp
 50 55 60

Met Cys Pro Pro Gln Gly Trp Gly Leu Glu
 65 70

<210> 626

<211> 198

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 626

gttgctgatc atggtcattg tactcgttgg ccatggatgt gtccaccaca aggttgggggt 60

ctcgaggggtt ccggttccgc aaccggcggc tctggctcca ctgcttcttc cggttccggt 120

tctgctactg gtgttgctga ccacgggtcac tgcacccggt ggccgtggat gtgcccgcgc 180

cagggttggg gtctggaa 198

<210> 627

<211> 70

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptibody

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> Xaa = Fc

<400> 627

Xaa Gly Gly Gly Gly Gly Ala Gln Val Ala Asp His Gly His Cys Thr
 1 5 10 15

Arg Trp Pro Trp Met Cys Pro Pro Gln Gly Trp Gly Gly Ser Gly Ser
 20 25 30

Ala Thr Gly Gly Ser Gly Gly Gly Ala Ser Ser Gly Ser Gly Ser Ala
 35 40 45

Thr Gly Val Ala Asp His Gly His Cys Thr Arg Trp Pro Trp Val Cys
 50 55 60

Pro Pro Gln Gly Trp Gly
 65 70

<210> 628
 <211> 186
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 628
 gttgctgatac atggatcattg tactcgttgg ccatggatgt gtccaccaca aggttgggggt 60
 ggttccgggtt ccgctaccgg cggctctggc ggtgggtgctt cttccgggtc cggttctgct 120
 actggtgttg ctgaccacgg tcaactgcacc cgttggccgt ggggtgtgtcc accacaaggt 180
 tgggggt 186

<210> 629
 <211> 74
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Peptibody

<220>
 <221> MISC_FEATURE
 <222> (1)..(1)
 <223> Xaa = Fc

<400> 629

Xaa Gly Gly Gly Gly Gly Ala Gln Pro Glu Ser Gln Gly His Cys Thr
 1 5 10 15

Arg Trp Pro Trp Met Cys Pro Pro Gln Gly Trp Gly Leu Glu Gly Ser
 20 25 30

Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly
 35 40 45

Ser Ala Thr Gly Pro Glu Ser Gln Gly His Cys Thr Arg Trp Pro Trp
 50 55 60

Met Cys Pro Pro Gln Gly Trp Gly Leu Glu
 65 70

<210> 630
 <211> 198
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 630
 ccagaatctc aaggtcattg tactcgttgg ccatggatgt gtccaccaca aggttgggggt 60
 ctogaggggtt ccggttccgc taccggcggc tctgggtcca ctgcttcttc cggttccgggt 120
 tctgctactg gtccggaatc ccagggtcac tgcacccgtt ggccgtggat gtgccccgccg 180
 cagggttggg gtctggaa 198

<210> 631
 <211> 70
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Peptibody

<220>
 <221> MISC_FEATURE
 <222> (1)..(1)
 <223> Xaa= Fc

<400> 631

Xaa Gly Gly Gly Gly Gly Ala Gln Pro Glu Ser Gln Gly His Cys Thr
 1 5 10 15

Arg Trp Pro Trp Met Cys Pro Pro Gln Gly Trp Gly Gly Ser Gly Ser
 20 25 30

Ala Thr Gly Gly Ser Gly Gly Gly Ala Ser Ser Gly Ser Gly Ser Ala
 35 40 45

Thr Gly Pro Glu Ser Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys
 50 55 60

Pro Pro Gln Gly Trp Gly
 65 70

<210> 632
 <211> 186
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding Myostatin Binding Peptide

<400> 632

ccagaatctc aaggtcattg tactcgttgg ccatggatgt gtccaccaca aggttgggggt 60

ggttccgggtt ccgctaccgg cggctctggc ggtggtgctt cttccgggtc cggttctgct 120

actggtccgg aatcccaggg tcaactgcacc cgttggccgt ggatgtgtcc accacaaggt 180

tgggggt 186

<210> 633

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Myostatin Binding Peptide

<400> 633

Trp Met Cys Pro Pro

1 5

<210> 634

<211> 90

<212> DNA

<213> Artificial Sequence

<220>

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<223> N = A, T, C, or G are equally represented

<220>

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<222> (18)..(18)

<223> K = G and T are equally represented

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<222> (19)..(20)

<223> N = A, T, C, or G are equally represented

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<223> K = G and T are equally represented

<220>

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<222> (22)..(23)

<223> N = A, T, C, or G are equally represented

<220>
<221> misc_feature
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<223> K = G and T are equally represented

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<223> K = G and T are equally represented

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<223> K = G and T are equally represented

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<223> K = G and T are equally represented

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<223> K = G and T are equally represented

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<223> K = G and T are equally represented

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<223> K = G and T are equally represented

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<223> K = G and T are equally represented

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<223> K = G and T are equally represented

<220>
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